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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

EIGHTH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 30, 31, AND JUNE 1, 1893.

VOLUME VIII.

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ASSOCIATION

OF

AMERICAN PHYSICIANS.

CONSTITUTION

As Amended May 30, 1893.

Article I.

Object and Name.

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II.

Members.

The number of active members shall be limited to one hundred. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III.

Officers.

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually;

five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV.

Duty of Officers.

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V.

Council.

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI.

Meetings.

1. The Association shall hold an annual meeting in the City of Washington, D. C., at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. Authors of papers, and referees and co-referees who open a discussion shall not occupy more than thirty minutes each; and in the discussion following the remarks of each speaker shall be limited to ten minutes.

5. The referees, co-referees, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII.

Quorum.

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum; and for altering the Constitution, twenty-five members shall be necessary.

ARTICLE VIII.

Election of Members.

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee, and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX.

Annual Dues.

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

ARTICLE X.

Amendments to Constitution.

Amendments to the Constitution must be proposed in writing by five members at an annual meeting and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendments; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

EIGHTH ANNUAL MEETING,

Held at Washington, D. C., May 30 *and* 31, *and June* 1, 1893.

THE following members were present during the meeting:

A. C. Abbott.
I. E. Atkinson.
A. B. Ball.
G. Baumgarten.
J. S. Billings.
M. Bolton.
C. S. Bond.
S. C. Busey.
W. T. Councilman.
W. C. Dabney.
William H. Draper.
R. H. Fitz.
C. F. Folsom.
F. Forchheimer.
J. P. C. Griffith.
H. A. Hare.
I. Minis Hays.
Henry Hun.
H. M. Hurd.
W. W. Johnston.
T. S. Latimer.
M. Longstreth.
A. L. Loomis.
S. Loving.
A. L. Mason.
S. J. Meltzer.
W. P. Northrup.
William Osler.
G. L. Peabody.
William M. Polk.
D. W. Prentiss.
T. M. Prudden.
J. J. Putnam.
B. Robinson.
F. C. Shattuck.
A. A. Smith.
Theobald Smith.
Louis Starr.
M. Allen Starr.
W. G. Thompson.
E. L. Trudeau.
James Tyson.
H. P. Walcott.
William H. Welch.
J. T. Whittaker.
J. C. Wilson.
H. C. Wood.

Tuesday, May 30th.

Morning Session.

The President, Dr. A. L. Loomis, called the Association to order at 10.15 A.M., and read the

President's Annual Address.

as follows:

Gentlemen of the Association of American Physicians: The length and promise of the programme, as arranged by the Council for the present session, leaves little but official duties for its presiding officer, and my feeling is that my best presidential contribution to this meeting would be to sit as a respectful listener.

But in accepting the honor you have conferred upon me I cannot refrain from availing myself of its associated privilege to say a word of introduction to the work that is before us.

No one who appreciates how fully the membership of this Association justifies its name can honestly discharge the duties of your highest office and ignore the obligations which rest upon us as a representative body. We have just celebrated, as nations count, our fourth birthday, yet the word American stands before the world for all that is most advanced in science. As we enter upon the new century-year it should be with the full appreciation that the theory and practice of medicine have given place to the science and art of medicine.

The nature of this change cannot be more tersely or aptly described than in the words of Ruskin: "The work of science is to substitute facts for appearances, and demonstrations for impressions," which plainly means that all our errors in science are subjective.

The day of speculative medicine has passed; henceforth we must know, not suppose; and whatever is offered in public must have the stamp "*Scio.*" In testing medical work by this standard, it is all too evident that we are called upon to undo as well as do. Even among accepted statements, we must own to many unsolved problems and unquestioned results that are but partial solutions, while we tacitly, if not openly, plead to a cowardly fear to say I *do not know*, when we cannot say *I know*. To this end there must be a clear consciousness of the boundary line between speculation and demonstration. The tripod support of science is, *observation, theory, demonstration.* The first gathers facts, the second considers their relations, and the third

tests all. He who offers observation alone, asks your judgment as to their accuracy and your help in determining their relations. If he adds an opinion regarding these relations, it is again to invite criticism and aid in the establishing demonstration, without which it is impossible to say that a new truth has been added to the science of medicine. But he who adds one such truth to our knowledge—a truth which all investigators are compelled to accept and make a part of their work must exert a powerful influence on medical advancement. Scientific skepticism is perhaps the most striking characteristic of medical investigation to-day; a skepticism which doubts not for the sake of doubting, but which demands proofs and counter-proofs; which scans facts, not men, and learns to recognize truth from whatever source it may come. As a legitimate result of this spirit there has been developed what is, without question, the greatest advance in methods ever made in medical science.

We have started afresh at the very rudiments of our science, and in the kindergartens of the laboratory are seeking to know the laws of health and the causes of disease; to have all theories based upon clearly determined facts, and use such theories only as guides to the discovery of the missing links in the chain of investigations.

The deductions of theories from a few isolated facts, and the construction of entire systems of medicine upon a single and often-improved assumption, were characteristic of the earlier ages of medicine. By how much is the medical mind different to-day. Under greater restraints, by reason of sharper criticism, with broader foundations, no such extensive speculative theories are offered for our consideration as mark the earlier history of medicine; but the same spirit remains as one of the heaviest clogs to the advancement of scientific medicine. Theoretical conclusions are still put forth, all too often as established facts, and not as questions demanding proof. This error seems to have its origin in failure to appreciate, or to have constantly in mind that objective facts are only manifestations of underlying forces, and that only through intellectual forces are these gross sensory impressions productive of scientific truth. Whoever thus aspires to have his work honored as scientific must never forget that, however accurate his data, or axiomatic his postulates, the value of final results, stand in direct ratio to the completeness as well as accuracy of his demonstrations, or lose sight of causative forces as the goal of all scientific work. We find an organ degenerated, and are content, forgetting that such an organ is only a lifeless proof of something done, and stop our ears to Science's query, "What was the force which caused this death?"

Our "pater amatres," Virchow, has pointedly indicated our duty in saying "that every man of science should set to himself the task of putting forth only what is actual knowledge; that whenever he goes beyond this he must always say: 'observe, this is not proven, but it is my opinion, my idea, my theory, my speculation.'" Many a one fails because he has not completely mastered the very material from which he attempts to draw his conclusions. Many an honest investigator fails because he does not realize how difficult it is for one man to comprehend all the details of the subject which he attempts to investigate. The final test of a scientific mind is its power of deciding, after any given demonstration, between legitimate conclusions and unfounded inferences.

When the medical history of the last half of the nineteenth century shall be written it will be largely that of the laboratory. Among the names which the twentieth century must honor none will stand higher than those who, having devoted themselves to establishing objective facts of medicine, were not beguiled by their work to elevate the experimental above the practical. Let us also, who are brought into such intimate relations with the practical, see to it that we are equally wise and self-controlled.

The experimental alone can never accomplish the great work that is ever before the physician. It essays, indeed, the solution of ultimate problems, and seeks to grasp the primal forces of disease, but it must, perforce, grapple with each one singly, never with all those infinite combinations which make up the sum of what we call disease.

We can never safely ignore the rich store of clinical facts gathered by so many master minds, or let them be withdrawn within the recesses of the laboratory. Although from the laboratory we hope to receive the solution of many problems which have long baffled us, it must be remembered that the special field of medical investigation is, and ever will be, disease in its activities. All its forces can be studied and understood only at the bedside of the patient.

Gentlemen, it is your privilege your duty; a debt to your fellow-workers waging unequal conflict with unseen foes, to speak "cum auctoritate." It is your reward to have your words stamped with the approval of the highest tribunal—a body of peers, giving impartial judgment. I bid you once more, take careful heed to the foundations of your tripod, nor forget that each foot stands by itself apart. Science rests not at the foot, but on the head, where accurate observation, comprehensive appreciation of relations between causative forces, and mathematical demonstrations unite in the unchanging laws of health

and disease, of life and death—a safe support for all your art, because its centre is the science of medicine.

Before entering on our scientific work let us linger for a moment to speak a word of tribute to those whom death has taken from us during the past year. We miss two whose companionship we were proud to claim—Dr. William Geddings and Dr. George Ross.

Dr. Geddings was a physician by inheritance, by birth, and by nature; and, although only in his fifty-fifth year at the time of his death, at Bethlehem, N. H., in August of last year, he had been in active practice for nearly thirty-one years. His life up to the time he established in Aiken, S. C., had been peculiarly one of study and training, in which he had become familiar with the medical work of Vienna, Prague, Berlin, and Paris. As medical purveyor of the Army of Virginia, in the Confederate service, he gained an unusual amount of practical knowledge, which was again supplemented by two years in the Imperial Hospitals of Vienna. On his return to this country he established himself at Aiken, S. C., where he soon became recognized as an authority in pulmonary diseases and climatology, upon which subjects he contributed many valuable papers to medical literature.

For many years Dr. Geddings suffered from a serious spinal affection, yet, even when the symptoms of diabetes developed two years before his death, his equanimity was not disturbed, but, with great fortitude, kept at his work to the last.

Dr. Geddings was a cultured gentleman, a skilful physician, a good diagnostician, and a most delightful companion. To his professional friends his sudden death came as a personal loss. By all who knew him intimately his memory will be affectionately cherished.

George Ross, Vice-Dean of the Medical Faculty of the McGill University, one of our original members, died in Montreal, May, 1892, at the age of forty-seven years.

In 1866 Dr. Ross graduated in medicine from the McGill University, taking the Holmes gold medal for general proficiency in all branches of the medical curriculum. Immediately after his graduation he entered the Montreal General Hospital, filling the position of house surgeon until 1872, when he commenced practice in his native city, and soon after was elected one of the attending physicians of the Montreal General Hospital, and received from the governors of the McGill University the appointment as professor of clinical medicine. He quickly became known as a successful teacher of medicine, a keen and careful investigator, and a sharp diagnostician.

In 1889, on the death of Dr. R. P. Howard, Dr. Ross was appointed

to the chair of medicine, and became Vice Dean of the University. As Representative Governor of the College of Physicians and Surgeons of the Province of Quebec he supported every measure calculated to increase the dignity of the profession and to raise the standard of medical education in the Province.

He contributed many valuable articles to medical literature, notably his articles on peritonitis and aortic aneurism.

Dr. Ross's whole career as a physician was passed without the slightest tarnishing of his brilliant and honorable professional record. His life was the best possible illustration of the happy union of the skilled physician and teacher with the accomplished gentleman.

Both these men did all that man can do. They did their part in life with faithful zeal until their powers gave way, and, with the wisdom which never dwells in sordid minds, they did not leave their mental wealth for legacies; but day by day transferred it to men with fresher strength, and gave over—not gave up—their work, content in the knowledge that it was not to cease, but grow larger year by year; and when at last their summons came, the best of all they had—the essence of the man, his quality—they left with us.

Both were in the prime of their years, yet their fifty-five and forty-seven years are added to those marks of death from which the years are slowly crystallizing out the deepest spirit of our work. At present the world calmly reads those lines of silent figures, and carefully says: "Yes, doctors' are the shortest lives of all the professions," and think no more of what that means. Perhaps the world will never stop to think; but in that day when all our books are closed, and other books are opened, who looks along the line until he finds "Physician" will look in vain for the small fraction of life's span, but may read instead: "He saved others; himself he did not try to save."

The minutes of the last meeting of the Association were accepted as printed in the TRANSACTIONS.

The Secretary read a letter from Dr. J. S. Billings, stating that he had been authorized by the Surgeon-General of the Army to extend the hospitality of a room in the Army Medical Museum and Library Building for the eighth annual meeting of the Association, which he did with great pleasure. It was resolved that the Secretary be instructed to transmit to the Surgeon-General the thanks of the Association for the courtesy which he had extended to it.

The resignation of Dr. Pepper, as Representative on the Executive

Committee of the Congress of American Physicians and Surgeons, was read and accepted.

Article VIII. of the Constitution was amended by inserting in the sixth line, after the word "publications" the words "The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same."

Article IX. of the Constitution was amended by striking out the words "fifteen dollars" and inserting the words "such sum as the Council from time to time may fix."

Dr. George Dock, of Ann Arbor, and Dr. T. M. Rotch, of Boston, were elected members of the Association.

A letter of resignation from Dr. Minot was read, and he was transferred by ballot from the active to the honorary list of members.

The Treasurer's report was read and referred to Drs. I. Minis Hays and M. A. Starr as an Auditing Committee.

Dr. Beverley Robinson then read a paper on "The Course and Treatment of Certain Uræmic Symptoms," which was discussed by Drs. Tyson, Johnston, Atkinson, Loomis, and Robinson.

In the absence of Dr. A. H. Smith his paper entitled "The Reaction of the Urine with Ether" was read by Dr. D. W. Prentiss.

The paper of Dr. C. W. Purdy, entitled "Detection and Significance of Proteids in the Urine," was read by title.

Dr. C. S. Bond then read a paper on "The Probable Origin and Early Symptoms of Certain Chronic Diseases of the Kidneys," which was discussed by Drs. Whittaker and Bond.

Dr. W. G. Thompson then read a paper entitled "A Study of Addison's Disease and of the Adrenals," which was discussed by Drs. Peabody, Welch, Whittaker, and Thompson.

Dr. James Tyson then read a paper entitled "Two Cases of Cystin Calculus," which was discussed by Dr. Whittaker.

Adjourned at 1.10 P.M.

Afternoon Session.

The Association was called to order at 2.45 P.M. by President Loomis.

Dr. G. Baumgarten read a paper on "A Simple Continued Fever," which was discussed by Drs. Atkinson and Baumgarten.

The paper of Dr. S. A. Fisk on "The Treatment of Typhoid Fever" was read by title.

Dr. J. T. Whittaker then read a paper on "Creasote in the Treatment

of Tuberculosis," which was discussed by Drs. Wood, Bond, Trudeau, and Whittaker.

Dr. F. Forchheimer read a paper on "The Intestinal Origin of Chlorosis," which was discussed by Drs. Griffith, Wood, and Forchheimer.

The paper of Dr. N. Bridge on "Coffee-Drinking as a Frequent Cause of Disease," was read by title.

Dr. H. C. Wood then read a paper entitled "Experimental Observations Concerning the Nature of Chorea," which was discussed by Drs. Whittaker, Welch, Osler, and Wood.

The Auditing Committee then reported that they had examined the Treasurer's report and vouchers, and had found them correct. Their report was accepted and the committee discharged.

Adjourned at 4.45 P.M.

WEDNESDAY, MAY 31ST.

MORNING SESSION.

The President, Dr. A. L. Loomis, called the Association to order at 10.10 A.M.

In the absence of Dr. F. P. Kinnicutt, the Referee, the discussion on Myxœdema was opened by the reading of his paper by Dr. Thompson, and was continued by the co-referees, Drs. J. J. Putnam and M. A. Starr. Dr. W. G. Thompson then read a paper entitled "Report of a Case of Myxœdema," and all four papers were then discussed in common by Drs. F. C. Shattuck, Welch, and Putnam.

Dr. William Osler then read a paper on "Sporadic Cretinism in the United States," which was discussed by Drs. Wood and Griffith.

Dr. Trudeau then presented some rabbits, showing the effects of tuberculin treatment and the immunity conferred by inoculation of the bird with bacilli tuberculosis, discussion on which was postponed.

Dr. T. Smith then read a paper entitled "Some Problems in the Etiology and Pathology of Texas Cattle Fever, and Their Bearing on the Comparative Study of Protozoan Diseases," which was discussed by Dr. Welch.

The paper of Dr. E. O. Shakespeare on "The Prophylaxis of Cholera, with Especial Reference to Immunization," was read by title.

Adjourned at 1.15 P.M.

Afternoon Session.

The Association was called to order by President Loomis at 2.50 P.M.

In the absence of Dr. H. C. Ernst, his paper entitled "A New Pathogenic Bacteria," was read by Dr. Welch, and was discussed by Drs. Abbott, T. Smith, and Whittaker.

Dr. A. C. Abbott then read a paper entitled "Experiments with the Bacillus Diphtheriæ," which was discussed by Dr. Welch.

Dr. W. T. Councilman then read a paper entitled "Gonorrhœal Myocarditis," which was discussed by Drs. Fitz, Tyson, Loomis, and Councilman.

The paper of Dr. Heneage Gibbes on "The Parasitic Nature of Cancer" was read by title.

Dr. S. Loving read a paper entitled "Acute Follicular Tonsillitis," which was discussed by Drs. Whittaker and Mason.

Dr. D. W. Prentiss then read a paper entitled "Sarcoma of the Lung, with Specimen," which was discussed by Drs. Welch, T. Smith, Trudeau, and Loomis.

A discussion on Dr. Trudeau's paper of this morning was then opened by Dr. Welch and continued by Drs. Whittaker and Trudeau.

Adjourned at 5.45 P.M.

Thursday, June 1st.

Morning Session.

The President, Dr. A. L. Loomis, called the Association to order at 10.20 A.M.

The nominations for officers of the Association made by the Councillors were read by the Secretary.

The paper of Dr. G. M. Garland on "The Importance of Uterine Displacements in the Production of Vomiting during the Early Stages of Pregnancy," and the paper of Dr. William M. Polk on "Uterine Drainage in the Several Forms of Inflammation of the Uterus and Its Appendages," were read by title.

Dr. James C. Wilson then read a paper on "Pulsating Pleural Effusions," which was discussed by Drs. Osler, Mason, Loomis, Fitz, and Wilson.

Dr. A. L. Mason then read a paper entitled "Subphrenic Abscess, with Especial Reference to Cases which Simulate Pneumothorax," and Dr. S. J. Meltzer read a paper entitled "Subphrenic Abscess," and

both papers were discussed in common by Drs. Osler, Welch, Fitz, and Mason.

The paper of Dr. James Tyson, entitled "Two Cases of Diaphragmatic Hernia," was read by title.

It was resolved that the papers which had been read by title at this meeting be published in the volume of TRANSACTIONS.

The following officers, nominated by the Council, were then unanimously elected:

President.—Reginald H. Fitz.

Vice-President.—William Osler.

Recorder.—I. Minis Hays.

Secretary.—Henry Hun.

Treasurer.—W. W. Johnston.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons.—William H. Welch.

Alternate Representative.—M. Allen Starr.

Councillor.—John H. Musser.

Adjourned at 12.20 P.M.

HENRY HUN, *Secretary.*

NOTICE.

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

ON THE COURSE AND TREATMENT OF CERTAIN URÆMIC SYMPTOMS.

By BEVERLEY ROBINSON, M.D.,
OF NEW YORK.

In beginning my paper I wish to say that I am in doubt as to the title of it. In some respects I would prefer to use the designation "symptoms of renal insufficiency, or inadequacy" rather than "uræmic symptoms." I make this statement because *uræmia* does not satisfactorily express, as we all know, our belief to-day in regard to the precise etiology of many cases in which the kidneys are no doubt at fault primarily or secondarily. If, however, I employ the designation *renal insufficiency*, I feel that exception may be taken to the title, as I shall speak of cases in which the kidney is surely affected with well-defined structural changes, and the term uræmia, as it is generally received, implies this belief in the majority of instances.

In my daily routine, especially of private practice, I meet with cases of the kind I shall at first try to describe, and with which doubtless you are more or less familiar. The patients to whom I refer are, as a rule, what are called healthy, *i. e.*, they have no distinctly marked organic changes which are discoverable in their different organs; or these changes are so slight in amount that I cannot fairly attribute major importance to the state of one organ as compared with the others, without the most careful analysis of all the conditions involved. Such patients, however, have habitually some little bodily annoyances which fret them more or less, and from which they desire to be relieved, and naturally seek, sooner or later, the physician's care. In regarding these patients at present, I am satisfied that many of them suffer primarily from slight renal disorder. This affection of the kidneys, mainly functional, is at times more

pronounced, and occasions symptoms which hitherto we have considered under the term uræmic.

In the mildest forms of the trouble, I believe renal insufficiency is a more appropriate term, particularly if we limit its proper significance. I am aware that the term itself is frequently employed in descriptions of uræmia, although I have not found an article or chapter in which the epithet was used as the *title* of a recognized condition. By adopting this name with this purpose, we shall be able hereafter to employ it to cover a definite series of symptoms, which, in my judgment, are not otherwise properly designated.

I will now narrate a few cases in my later professional experience which shall serve as a text to explain my position.

CASE I.—A lawyer; widower; fifty-five years old; is a man of large frame, who has enjoyed excellent health. In the winter months he suffers from nasal obstruction and formation of excess of mucus in his naso-pharyngeal space, which he relieves by efforts of hawking. Patient has a somewhat constipated habit, and his urine is often higher colored than is normal. Frequently, however, the density and color are normal. It contains at these times no abnormal ingredient. Whenever the density increases and the color is darker, there is a heavy deposit of pink urates; but there is no albumin, no sugar, and rarely, if ever, any casts. The quantity of urine voided, as a rule, approximates the normal. When the color becomes dark and the density increases, the quantity diminishes, but not usually to any great extent. Patient under the latter circumstances suffers from general neuralgic manifestations, mild in form and which rapidly disappear under judicious medical management. Appetite is excellent; no dyspeptic symptoms ordinarily; lives well, but commits no excesses. Very moderate in the use of wines or distilled liquors. No attacks of rheumatism or gout. Patient finds he is much better in health when he eschews sweets and butchers' meat; feels more buoyant and in better shape when his meals consist mainly of vegetables, and particularly rice, and when he eats white meats, fresh fish, and eggs. On several occasions, I have attended him professionally, when, without knowledge of the precise cause of his attack, he has had sneezing and running of the nose; little or no fever; slight cough; no evidences of stomachal derangement, and yet he was evidently torpid or sluggish and complained of marked drowsiness. The urine at these times was dark-colored and loaded with urates. A mercurial, followed by a brisk saline purge, on two successive days, rest in the house, the free use of natural Vichy water, and very light diet, cured these manifestations of disordered function, and in a few days he resumed his occupation and was as well as previously.

CASE II.—A broker; forty-two years old; married; thin and spare; of an energetic, resolute character; states that several years ago he passed a small mulberry calculus, but previous and subsequent to this attack has had no dis-

ease in many years. His urine is habitually somewhat high-colored, otherwise normal; his intestinal digestion is imperfect; he is somewhat constipated at times; again he has two movements in the twenty-four hours, which are formed, but not as large as would seem to be healthful—due regard being had to the amount he eats. His diet is varied, abundant, but not excessive. He drinks wine moderately; he smokes, but not to excess. He is often annoyed with vague pains in his abdomen which extend into the lumbar region. These pains are not severe as a rule, and usually are merely uncomfortable sensations. His abdomen is perhaps slightly distended and tense, but he is scarcely annoyed with flatus. The epigastrium is somewhat tender on pressure, as also, occasionally, are other regions of the abdominal cavity. There is no manifest stomachal dyspepsia. The vague abdominal pains come at irregular intervals during the day, last a variable time, and disappear quite suddenly. Patient is rendered irritable and somewhat morbid by reason of his abdominal condition. He is also conscious of a slight laryngeal irritation which obliges him to expectorate a small quantity of viscid phlegm occasionally. His tongue is broad, slightly coated on the dorsum; his skin is sallow; his liver is not enlarged. Strict regulation of the diet, as in the previous case, the regular use of euonymin, podophyllin, or cascara, persistent drinking of Giesshübler or Vals water, have ameliorated but not cured my patient. Latterly, I have prescribed salicylate of bismuth in addition to what precedes, with the hope that intestinal antisepsis thus produced would be effective in controlling the symptoms of functional disturbance which I have outlined and which I have been led to believe were caused by renal insufficiency.

CASE III.—Only a few weeks since I was called suddenly to see a near and dear relative, who had been attacked with alarming symptoms of obstinate nausea and vomiting, marked cardiac weakness, and with but few or no evidences in the urine, except just before the fatal termination, of renal complication. At this time a small quantity of albumin and hyaline casts were discovered. The patient was fifty-eight years old, the manager of important railroad lines. He had always been remarkably strong and active. Owing to great irregularity of meals and the immoderate use of tobacco and whiskey, he was a sufferer frequently from flatulent dyspepsia, which he relieved with large doses of bicarbonate of soda. Some weeks previous to his death he had an attack of pneumonia, moderate in severity. From this attack he had nearly recovered, when, by reason of over-fatigue, anxiety, and exposure, a mild invasion of acute articular rheumatism developed. The fever had disappeared and he was almost convalescent from this disease when, owing to the immediate effects of a cold bath, the final symptoms occurred, and were regarded by the family physician as evidences of Bright's disease. When I saw this patient I thought the kidneys were congested, but secondarily to the action of a weakened heart, and were connected with engorgement of the other viscera under a similar dependence. This was eminently true of the lungs and liver. No doubt it was the giving way, functionally, of several important organs, which caused this patient's death. Whilst this is true, it

is also highly probable that the condition of the kidneys, which had become more and more insufficient, gave the terminal features of the combined conditions, to a greater degree than any one, or all, of the other organs involved.

CASE IV.—A broker; bachelor; thirty years old; of a nervous, excitable temperament; suffers somewhat from symptoms of flatulent dyspepsia and irritable heart. His bowels are frequently torpid; his urine habitually slightly high colored; habits temperate—drinking little; does not smoke; no gout or rheumatism. After an elaborate dinner at which he drank different wines—but not to the point of inebriety—he went home and slept. In the early morning he had repeated attacks of vomiting and diarrhœa. Accompanying these symptoms there was moderate headache and annoying palpitations. His pulse was rapid, weak, depressible, and irregular. His heart action was also much disturbed; it was rapid, irregular, and the impulse weakened. There was a soft systolic bruit accompanying the second sound over the pulmonary area. Apparently the cardiac cavities were somewhat dilated. The tongue was clean, and yet nausea was distressing. No tenderness over the epigastrium, or anywhere in the abdominal cavity. The urine had been smaller in quantity since the night previous, and instead of being dark in color, was very light. Under the use, first, of ammonia and bismuth, with broths, milk, and Vichy, and rest in bed, he improved rapidly. His heart grew stronger; his urine became more concentrated and larger in quantity. When the first symptoms disappeared, strophanthus and nux vomica were added to the previous treatment.

Such cases as the foregoing may be differently designated, I am quite aware, and at times are considered of little moment and scarcely worthy of very careful consideration. I have known many such attacks regarded as the usual outcome of excesses of the table and put down in the broad category of a bilious attack. In one sense they are, without doubt, if we mean by that to express the idea that the liver is incidentally interfered with as to its physiological function; but while this may be true, I claim *now* that such cases are correctly interpreted in recognizing that the kidneys, by their temporary insufficiency, occasion most of the symptoms reported, in a very direct manner. It is also evident that strengthening the cardiac contractions and giving more vascular tone to the general circulation will be found useful. These indications may indeed be urgent. Is it not obvious, however, that it is the retention in the economy of the waste substances, made suddenly enormous by reason of dietary indiscretion, which brings on the threatening symptoms which require relief by all rational methods? Nature makes every effort in these cases, by frequently repeated vomiting and purging, to clear the

body, through these natural emunctories, of the poisonous fermenting ingesta which enter so largely as a factor in the direct causation of such explosions. The rest in bed; the gentle and continuous warmth to the surface; the liquid diet, which is the most rational diuretic as well as food, the quieting effect of the ammonia and bismuth on the irritated stomachal mucous membrane, and the stimulating influence of the former in relieving general depression, were rapidly followed by beneficial effects. As soon as practicable the heart was strengthened and regulated to overcome the effects of diminished arterial tension throughout the body, but particularly in the kidneys, whose functions should be re-established in order to restore equilibrium to the economy.

CASE V.—A maiden lady, forty-five years old, thin and spare of body, passed her menopause without functional disturbances; she has always been healthy and vigorous; has a good appetite and digestion; bowels regular; heart action normal; no malaria, rheumatism, or gout. Patient suffers from obstinate, recurrent headaches every morning. After she awakens, gets her coffee and a light breakfast, they frequently disappear, or become less intense. At times they continue during many hours of the day, and only disappear completely, without apparent cause, to return again the following morning. The urine is normal in quantity, rather light in color, containing no abnormal substances. In this case there was no cardiac hypertrophy and no increased vascular tension, at least, neither one nor the other, that could be affirmed after careful examination. Almost every rational explanation of the headaches was attempted, and on each occasion followed up by appropriate treatment of the supposed cause, without beneficial effect. Finally, I thought that imperfect elimination of the products of disassimilation through kidneys functionally insufficient, and which possibly were affected with the precursory stage of interstitial nephritis, might account for the headaches. Thereupon I prescribed nitroglycerin in the ordinary dose of one minim of a one per cent. solution every four hours, and very soon the headaches were relieved, if not cured. I now felt tolerably sure that my interpretation of the case was correct.

I might multiply examples of different kinds pointing to what I would call insufficiency of renal excretion, with many minute details, but this narrative would merely prove wearisome.

In many instances of obstinate nasal, naso-pharyngeal, laryngeal, and tracheal inflammation, chronic in type, I am now firmly convinced that the inactive functional condition of the kidneys is the primary cause of these inflammations. An imperfect blood-supply,

containing in it many elements which should be eliminated through the kidneys, is rendered a source of morbid manifestations in the whole mucous tract—sometimes of the respiratory organs, sometimes of the organs of digestion and assimilation. Doubtless, also, the renal congestion which originates, as it were, this vicious circle is heightened and made more intense by the blood loaded with excrementitious substances, which come to the kidneys continuously, and which, provisionally, they are unable to get rid of. In such cases I have often found, after the bowels had been freely moved, the mucous linings which could be reached with suitable topical applications had been properly treated, that a diuretic solution, such as the liquid ammonia acetatis, frequently given, produced the happiest results after it had been taken during several days in a regular manner.

I have noticed the preceding conditions on several occasions follow bad colds, of the nature of la grippe, or attacks of influenza, and in these instances have assumed that the specific nature of the disorder of the respiratory tract and general system had much to do with the evidences later on of renal insufficiency. In other cases in which there could be no doubt, in my own mind, that there were organic changes in the kidneys of the nature of chronic parenchymatous or interstitial nephritis, by reason of the specific gravity of the urine, the deposit of albumin frequently contained in it, and the frequency with which different kinds of tube-casts were found on microscopical examination, I have found the symptoms referred to in the cases reported, but seemingly of graver significance, because they were united with manifest organic renal changes. Almost invariably, as we know, all undue fatigue, intense emotional excitement, errors of diet or drink, cold and exposure, will aggravate renal disease and bring on rapidly, or slowly, disquieting symptoms. Knowing the previous condition of the kidneys, we can never prudently ignore this knowledge when we care for such patients.

CASE VI.—A distinguished architect of New York has been one of my patients, off and on, for at least eighteen years—indeed, during nearly all my professional life. This gentleman, now over sixty years of age, has had great industry, great talents, and remarkable professional success. Once or twice in the course of every year he has an acute gouty attack affecting the meta-tarso-phalangeal joint of the big toe of one or other foot. Sometimes these gouty attacks in the small joints of the feet come on without premonition;

sometimes a bronchial or slightly asthmatic attack precedes them. During the whole period I have taken care of this patient he has had urine light in color, of low specific gravity, containing a variable quantity of albumin and some granular and hyaline casts, whenever his bronchial, or, frankly speaking, gouty attacks are upon him; and in view of my knowledge of the condition of his kidneys, I am always very solicitous in regard to their outcome. I have seen him when the thoracic oppression was very intense, the heart beating irregularly, rapidly, and feebly, and the pallor and pinched expression of the face were striking and alarming. Accompanying this condition there were disseminated moist and sonorous râles in the chest, and the urine looked almost watery and was diminished notably in quantity. Under these circumstances I have found that repeated doses of colchicine and the free use of Friedrichshall water were the most useful medicinal remedies to employ. Rest in bed and fluid diet were insisted upon, and in some instances counter-irritation or revulsion to the back was deemed advisable. Subsequent to such attacks, giving up business affairs and travel were strongly favored, and when indulged in, rapidly brought about a state of well-being and the return to usual conditions.

In the evident gouty cases, and particularly in those where the heart action is good and the tension in the arteries not excessive, colchicine is a more valuable remedy than nitroglycerin. In instances, on the contrary, in which the arterial tension is well marked or excessive, and the heart laboring, whilst the quantity of urine is small and of low specific gravity, I believe it is wise to begin treatment with nitroglycerin or the nitrites. In any very alarming expression of this condition, inhalations of nitrites of amyl should first be employed. We shall sometimes be disappointed in the efficacy of these agents, and it is, I believe, whenever we have been committed to the error of believing that there is hyper-tension in the peripheral arterial system, connected or not with spasm in the vessels of the kidneys, or some other important viscus. Frequently, the so-called increased arterial tension is merely the consequence of atheromatous thickening of vascular walls, and the blood, instead of being under too great pressure, requires increase of the *vis a tergo* to make it circulate more freely and with greater energy. This may often be attained by the use of caffein or digitalis, and as a result of the effective use of one or both of these remedies, we are forced to conclude that the renal phenomena proceed directly from an enfeebled heart, and the true way of managing such cases is really not to make so direct an appeal to the kidneys, in the first place, but rather to the muscular heart-structure. In strengthening the latter, we help the former in a much

more obvious and important manner. When, however, we are not quite sure to what extent the kidneys originate the series of pathological events and also tend to keep them up, it is judicious to watch very carefully the administration of digitalis. I am convinced that whenever the renal function is markedly insufficient and the urine is greatly diminished, or perhaps wholly suppressed, we are liable to have those curious phenomena in the heart-beats and in the pulse, not to speak of nausea and vomiting, which show accumulation of this drug and its poisonous effects upon the economy. In many instances it is relatively simple to distinguish, in a differential way, the part played by the two conditions relative to cause and effect. In others, we are left in great and reasonable doubt, and our judgment in the matter remains most uncertain.

In regard to the simple question of the amount of arterial tension in the radial arteries, I know of nothing more difficult at times than to accurately estimate it—one reason being, besides the one already given, the amount of soft tissues about the artery at the wrist. Even with the use of the sphygmograph we may be unable to decide the matter, for the simple reason that tracings with this instrument are only valuable when made by an expert. Otherwise, we are liable to run into very great errors of interpretation. This is mainly due to the fact that it is very difficult to fit the instrument on any wrist so that we can form a perfect estimate of the directness and accuracy of its pressure over the artery.

Case VII.—A widow, of large bulky frame, about sixty years of age, takes very little exercise, but drives a great deal and lives most of the time in the open air, in summer at Newport, in winter at Cannes. Patient is careful with her diet, as a rule, but commits occasional imprudences in eating rich, or sweet food; almost invariably she pays the penalty of these errors by nausea, stomachal distress, pallor, and a sub-icteric hue of the skin. The pulse becomes weak, rapid, and depressible, the heart action fluttering and feeble; sometimes the bowels are torpid; sometimes there is and has been more or less diarrhœa, amounting to several loose movements in the twenty-four hours. I have known the attacks once or twice to be of a different kind; instead of the previous symptoms, the head ached intensely; there was torpor and somnolence; the speech was thick, the ideas came sluggishly; the face was somewhat drawn down on one side; the pupils were contracted, and there was more or less nervous irritability, as shown by slight fibrillary muscular twitchings. Seven or eight years ago, at the period of these latter symptoms, the urine was ordinarily of low specific gravity, moderate or

abundant in amount, and containing a small quantity of albumin and granular casts. Although the patient had been told that her condition was gouty, and this was true in a certain sense, yet she had never had either a frankly determined attack of gout or rheumatism. Compound cathartic pills, strophanthus, digitalis, and nitroglycerin have all been useful at times, and singular to say, the use of Warburg's extract has sometimes enabled me to be of the most manifest benefit, when the other agents completely failed. I suspected, therefore, very strongly, a malarial element, without, however, being able confidently to affirm it. Sometimes I have thought it possible that Warburg's extract was useful simply as an hepatic stimulant, and thus helped notably to relieve evident uræmic phenomena. Whenever I had gotten rid of the threatening phenomena in this case for a time, I insisted upon a milk diet, koumyss, matzoon, milk and Vichy, etc.; massage daily, or every other day; oxygen inhalations and repeated doses of digitalis in tablet triturate form. Every winter and spring, for several years, I have sent her to the south of France, and thus far she has held her own, and, indeed, I should say to-day, she is in better physical condition than she was several years ago.

In the preceding case and the one narrated before it, I have more than once seen what I believed to be evident and pernicious effects resulting from the use of even small doses of opium or morphine in some form—given by the mouth, for I have never had occasion to resort to the use of morphine hypodermically in either of the preceding cases. One of the interesting features in my last case is this: During the past two years the character of the urine has changed in a remarkable manner; as a rule, this is no longer light-colored, of low specific gravity, containing albumin and granular casts; on the contrary, it is of a fairly deep color, does not generally contain any albumin, and on several occasions has shown no casts when examined very carefully and by expert microscopists. What is my conclusion? Have I cured a case of interstitial nephritis or not? I will not pretend to solve this difficult question. I would simply report a very interesting clinical fact in my own private experience, of which there may be many in that of my listeners, so far as I know.

I now wish to speak of the use of opiates, and more particularly of morphine in these latter cases, whenever respiratory or other symptoms, such as obstinate or distressing insomnia, seem to require their employment. Personally, I am and always have been much opposed to the use of opiates, and especially of morphine hypodermically,

whenever used in cases of chronic Bright's disease, except in very minute doses. I believe I have seen it do harm so often in locking up the secretions, when just the contrary was imperatively required, in bringing out further symptoms of uræmia, acute or chronic, that it appears to me reasonable to abstain from this medication as long as possible. If its use is forced upon me by symptoms that I have vainly endeavored to relieve by other drugs which are more innocent in their effects, I always make use of it with great care and watchfulness. There are times, however, when I do not feel in this way, and where uræmic symptoms are unquestionably manifest. In general terms, these are the cases in which the heart is the weak organ primarily, and in which the kidneys will be greatly helped by cardiac stimulation of an active kind.

Of the numerous drugs which strengthen, quiet, and regulate a weakened, dilated heart, none at times is comparable to the hypodermic use of morphine in small or moderate doses. Therefore, when this condition is obviously the cause of the distressing or threatening symptoms, I am not unwilling to recur to its use. If blood-pressure is low, as shown by slight, imperfect arterial tension in the radials, and if the pupils are normal or somewhat dilated, with the previous condition also clearly defined, I am not averse to morphine medication in the manner I have mentioned. Unquestionably, when thus employed, I have had no good reason myself to regret making use of it. When, however, with the weak, irregular, or failing heart, are also present the pulse with lowered tension and the contracted pupil, then I would cry *halt!* because I believe these conditions often mean poisoning from retention in the system of excrementitious substances of different sorts, and more or less poisonous, which may rapidly overwhelm the economy in their disastrous effects, unless the clear indications of treatment are distinctly made out and followed by the practitioner. Again, in cases where we are in great and legitimate doubt—as we frequently are—despite our most careful scrutiny of a given case, as to which organ, the heart or the kidneys, most evidently needs immediate help—in these cases I advise against morphine hypodermically as long as possible, on account of the possible immediate and great harm which may follow its use.

Alongside of these cases, and as a further development of similar underlying conditions, is what we often see, *i. e.*, uræmic convulsions

actually take place. The quite general teaching of more than twenty years in New York City, owing perhaps more to Prof. Loomis' influence as a very prominent clinician than to anyone else, has been to the effect that morphine hypodermically in large and repeated doses in acute uræmia has done what no other drug with which we are familiar will do. It will bring the convulsive seizure to a rapid termination; it will at times prevent the recurrence of it; it will break up arterial spasm, it will thus lessen arterial pressure; it will promote diaphoresis; it will greatly increase the bulk of the urine when this secretion is diminished or almost suppressed; it will bring back to life when hope seems almost lost.

In view of the facts so graphically and forcibly brought to our attention by Dr. Loomis—narrated with all the clearness, talent, and ability which characterize his work—we should be loath to throw aside the instruction afforded by the close study of his cases. Inasmuch, however, as I have seen, I believe disastrous results follow this kind of interference; and when these results could not, in my judgment, be properly explained by the natural development of the renal disease, it is only right that I should endeavor to seek for the cause of this discrepancy. I have allowed my reasons to be seen in part in my foregoing remarks, and I would further add that whenever the convulsive seizure of acute uræmia is evidently directly occasioned by a spasmodic condition of the vessels of the kidneys, and this spasm is more or less general in the bloodvessels of the body, including in many cases the cerebral mass and the medulla oblongata, I have little doubt that the remedial effects of morphine injections, in tiding over a most critical period of disease, are very remarkable. But let us bear in mind, as the perusal of Loomis' cases and numerous others will distinctly show, that the convulsive seizures were accompanied with *dilated pupils* and a more or less disturbed, perhaps weak, heart action. Moreover, in the coma which habitually follows just such attacks, after the use of morphine, or sometimes, indeed, without its use, the pupil may become of pin-hole size, or very much contracted; the heart may be laboring just as much, or even more, and the kidneys may not secrete an increased quantity of urine. I regard such cases as being among those in which the system is even more overwhelmed with the so-called

uræmic poison than the previous ones, and to which I would fain direct closest attention.

In this translation of the immediate or prolonged effects of renal insufficiency, of systemic poisoning thus occasioned, whether occurring in Bright's disease or in mere functional disorder, we must look to several concealed factors involved in the clinical estimate which we should make. In one aspect, the kidney is nothing more than an ordinary filter; in another, it is an *elective* filter, depending, no doubt, for this power in part upon the precise anatomical and pathological conditions affecting it; depending also upon dynamic or vital forces, in regard to which we are almost in the dark even at the present day. Suffice it to add, however, that strictly scientific investigations, more particularly of Feltz and Ritter and of Bouchard, have shown how various are the poisonous ingredients of the urine, and how it is that at different times the kidneys will allow some of these poisons to pass through them, and again will not. Besides, the effects of the retained poisons are very different according to their nature—some doubtless accounting more than others for the pupillary and nervous symptoms; some producing excitement, others depression, lowered temperature, somnolence, and torpor.

These different poisons may also be eliminated from the economy even at short intervals in unequal amounts, and, of course, *different* morbid effects are thus produced, or similar effects in an unequal degree, in view of the combined nature or quantity of the retentions in the economy.

We should also be now convinced of another fact, and it is that neither the condition of the kidneys nor the heart, as shown by pathological researches, will prove satisfactorily, in many instances, the cause of the uræmic symptoms or seizures. We are, therefore, forcibly compelled to look for the source or primary cause of the symptoms elsewhere, and it is often in the digestive tract that we shall most certainly find them. The control of the quality and quantity of the ingesta; the proper and prolonged neutralization of poisons continuously produced in this system, will thus become a means of prophylaxis against uræmic developments of milder or greater intensity, which will be found second to none. So soon as the most urgent symptoms of acute uræmia are neutralized or antagonized, judicious antisepsis of the digestive tract is a treatment

which has the greatest value. Among drugs useful in carrying out this remedial indication, I would speak favorably, from repeated experience, of salicylate of bismuth and beta-naphthol.

In conclusion, I would add that I am convinced in very many such cases, especially among the residents of our cities, in the winter time, oxygen gas by inhalation several times daily, plays a very important remedial rôle. Banishment to a warm, equable climate for the cold or variable months of the year is, of course, generally speaking, a far better substitute than artificial inhalations of oxygen; but this plan, I regret to say, is often wholly impracticable.

DISCUSSION.

DR. TYSON: I cannot refrain from saying a word in support of Dr. Robinson's views as to the effect of opium upon chronic kidney disease, and its tendency, in my experience, to invite uræmia or the more tangible symptoms of uræmia, such as coma or convulsions. I have seen two drachms of paregoric cause an old man to pass into coma from which he never arose, and I have seen other cases of the same kind. I am very fully aware that morphine is recommended very highly in the treatment of uræmic convulsions, and also of Dr. Loomis's partiality for that treatment. Nor can it be said that such treatment is not efficient. Anyone who reads the journals will see almost daily reports of cases of the uræmic convulsions of puerperal nephritis successfully treated by hypodermic injections of morphine. I have no doubt that this is the case, for I have confidence in the men who report the cases. On the other hand, it is true that lives have been sacrificed to it. Naturally I have been caused to think about this question, and to endeavor, if possible, to separate the class of cases which are harmlessly treated by morphine and the class of cases in which morphine is dangerous, and it has seemed to me that the difference lies in the nature of the local kidney process. I think many will bear me out in the statement that it is in chronic interstitial nephritis that morphine is dangerous. It was in cases of chronic interstitial nephritis where the administration of opium was followed by such unfortunate results in my experience. On the other hand, cases of puerperal nephritis are well known to be, for the most part, cases of parenchymatous inflammation of the kidney, and I know from my own experience that morphine is borne better in this form of kidney inflammation than in cases of interstitial inflammation. Exactly why this is I do not know, but my own experience, I think, sustains this view, that morphine may be used with less danger in parenchymatous inflammation than in interstitial inflammation.

DR. JOHNSTON: I have been very much interested in Dr. Robinson's paper, as it is an able effort to elucidate phenomena that we so frequently observe in practice. The class of cases which he describes seems to me to be very common, and more so than formerly. Whether it is that city life and lives of ease are increasing these cases, I do not know. About eighteen months ago I read before our local medical society a paper in which I presented cases almost exactly analogous. I tried to present some theory as to their nature, and it seems to me that the conclusions which I reached are very much like those attained by Dr. Robinson, except that I gave rather greater prominence to the intestinal condition as the primary cause of the diseased state. In considering these cases we have to recognize this fact, that physiological variations precede pathological conditions, and that for quite a long time before these people develop any pathological lesion they have physiological variations. If we look at the history of these cases, it seems to me that the first condition we observe is one of over-feeding and intestinal indigestion. The history of the cases which Dr. Robinson has given shows the patients to be all persons enjoying ease of life. The case of a widow he reports is rather a typical one, living in Newport in summer and Cannes in winter, who doubtless had the best that wealth could afford. She had intestinal indigestion, with the loading of the blood with the products of an excessive albuminoid diet and also impaired albuminoid digestion. She then had renal disturbance as a result of this, and then cardiac disturbance as a result of the renal disturbance. I think that there is no doubt that the primary source of these disturbances is situated in the digestive tract. It is the accumulation in the blood of the morbid products of digestion that starts the train of phenomena. I have no doubt that in many of these cases, such as Dr. Robinson describes, the explosions are due to renal inadequacy, the result of the inability of the kidney to excrete these excessive, altered albuminoid products. If we are to believe the physiological chemists as to the results of intestinal decomposition in developing toxines in the intestine, it seems to me that another cause may explain some of these acute attacks, namely, that they are the results of acute absorption of toxic matters from intestinal fermentation. Some of the symptoms are too sudden in their onset to be due to renal inadequacy. They are associated so closely with attacks of intestinal indigestion, and with unusual excesses at the table, that they appear to be due to absorption of toxines from the intestinal canal.

DR. ATKINSON: I wish to say just a word in regard to the use of opium in uræmic conditions. I believe that there is no therapeutic fact more capable of demonstration than the extreme value of opium, or the hypodermic use of morphia, in the treatment of dangerous uræmic symptoms, especially in the sudden and acute œdemas of the lungs that come on in the course of contracted kidney. I do not know that I ever feel therapeutically more powerful than I do when I am brought to face the early attacks of œdema of the lungs in the course of contracted kidney. I feel that within five or ten minutes after administering morphine hypodermically I will see the sweat diminish, the cyanosis

disappear, the breathing become more quiet, and in the course of half an hour or so the patient will be restored to his usual condition. This I consider to be a matter that is perfectly capable of demonstration. It seems a little strange that where we can relieve very promptly, by the use of morphine, a condition of extreme distress and danger, that this same therapeutic measure could be so dangerous in conditions of mild renal insufficiency—a very dangerous remedy when the degree of toxæmia is mild, and a remedy of great value when the degree is extreme. I do not mean to say that opium is not a dangerous remedy in some cases of uræmic poisoning, but I cannot say so from my own experience. The testimony shows that dangerous symptoms do sometimes succeed the administration of small doses of morphine, but I think the explanation may often be found in this fact, that we are called to cases of mild degree of uræmic symptoms, in which the symptoms are increasing and will increase, no matter what we may use. The severe symptoms may follow the administration of a mild opiate, but are not in consequence of it. A point that I wish to emphasize is, that when this condition of uræmia is extreme we have in morphine, administered hypodermically, the most powerful remedial agency that can be offered.

DR. LOOMIS: When I brought the hypodermic use of morphia for the control of acute uræmia before the profession I stated very positively in my paper that it was for acute uræmia, and not for chronic, and for those cases of acute uræmia where there was no knowledge of any previous renal disease, such cases as we see in acute parenchymatous nephritis in the various infections, and which occur in connection with exposure to wet and cold. Those that came on during childbirth were particularly the cases which I brought before the profession as being relieved or controlled by that plan of treatment. Afterward I found that it was being used in cases of chronic uræmia, which I regard as an entirely different condition from that which I described as acute uræmia. The reports of the cases in which it has been used do not give definite information, because the cases are not distinctly differentiated. If it is used indiscriminately in chronic uræmia, a great deal of harm may be done. Only in those cases of chronic uræmia where you have a large and dilated heart, and where œdema of the lungs occurs partially on account of the uræmia and partially on account of the condition of the heart, should opium be used, and in these cases opium is a power because it controls the heart. In ordinary symptoms of renal insufficiency, where there is little if any structural disease, and where there is commencing, perhaps, the first stage of fibrosis, opium must be used with the greatest care. You are likely to add to the toxic condition which already exists from a number of sources, such as the intestine, the liver, etc. In such condition you will, in most instances, injure your patient.

DR. ROBINSON: I had behind my paper a very strong conviction. I desired to be as complimentary as I could to Dr. Loomis in regard to his work on the treatment of uræmia by the use of opium; at the same time I must say that I

think his instruction, so far as the junior members of our profession are concerned, has been used so inconsiderately and so unwisely at times that I have time and again stood at the bedside of patients in my ward who had been treated by the younger physicians, and felt that a great harm had been done. I have tried to point out to these younger gentlemen what I regard as the proper and broad treatment of these cases, and I have often been met with a smile. I nevertheless hold to my convictions. We know so little about the direct influence of structural changes in producing marked uræmia that at times when I go into the dead-house I feel as if I had better stayed away. I would like to refer those who are interested in the subject to an article written by Sir Andrew Clarke, in the *British Medical Journal* of February 24, 1883, entitled "Renal Inadequacy." This article made me feel what a great practitioner the author was. He endeavored to point out in his most forcible manner that we must look, after all, in our interpretation of the disease, to the functional derangement rather than to the pathological changes. As we all know, we go time and again into the autopsy-room and see cases which make us wonder how the man could live at all with so many different pathological lesions, and then again we see cases where macroscopic and microscopic examination shows nothing to explain the great suffering which the subjects had during life.

THE REACTION OF ETHER WITH URINE.

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For some years past I have been much interested in the question, to what extent alimentary substances may pass from the blood into the urine in healthy conditions of the kidneys. Familiar examples of such passage are found in the color or odor imparted to the urine by various articles of diet. It has seemed to me that albuminoid substances also might pass out by the kidneys and not be detected by the ordinary methods of examination, the form not being such as is precipitated by the agents usually employed.

We are apt to consider the organic matter in the urine as wholly the product of destructive metamorphosis, representing only material which has done duty as tissue, has become disintegrated, and is, finally, eliminated as waste. It appears to me, however, that, since the amount of nutritive material daily taken into the blood cannot be accurately apportioned to the prospective needs of the different tissues, their needs varying so widely under different circumstances of activity, there must be at all times in the blood a certain amount of potential tissue constituting a reserve which may, or may not, be called upon. If not called upon it would be eliminated, and some of it, probably, by the kidneys.

Starting with only the general proposition of the text-books that egg albumin is precipitated by ether, while serum albumin is not, I began a search for egg albumin in cases of suspected nephritis. My experiments brought unlooked-for results, but not at all in the direction anticipated. It was not in albuminous but in perfectly normal urine that a surprise awaited me. If we take a number of specimens of urine from presumably healthy persons, filter and agitate

very thoroughly with one-half or one-third, in bulk, of ether, we shall find that in most cases a mixed fluid results which is white and opaque and more or less foamy at the top. If, now, the test-tube be tightly corked and set aside, a separation gradually takes place, beginning at the bottom. This progresses until a sharp line of division is formed, below which is the clear urine, and above which is a gray, gelatinous stratum with, perhaps, some clear ether on the surface. This opalescent, gelatinous material may be so dense and adhesive as to allow one to turn the tube upside down without disturbing the contents, or even to require some shaking to dislodge it.

I have said that this reaction occurs in most instances, but in perhaps one-fifth of the specimens we shall find that the ether will not mix with the urine, even with the most vigorous and prolonged agitation, but instantly rises in a clear layer to the top. There may be, perhaps, a thin white line between the two fluids, but nothing of the gray gelatinous substance already mentioned. If, however, we add a few drops of an acid, preferably acetic acid, and shake the tube again, we may get the reaction which before was absent. Still, in a certain small proportion of cases, even with the addition of the acid, no reaction can be obtained.

Now let us remove the coagulum, by filtration, from a portion of urine that has given the reaction with ether alone, and then add acetic acid to the filtrate and agitate with a second portion of ether. This will always, so far as my experience goes, give a second precipitate in every way resembling the first.

We have now got so far that, with reference to this test, we may divide all specimens of urine into three classes: first those which give no reaction with ether without or with the addition of acid; second, those that give a reaction when acid is added, but not without; and third, those that give a reaction with ether alone, and again a second precipitate when acid is added. In the latter case it is evident that two substances are present, one that responds to ether alone, and another that responds to ether plus an acid. To avoid frequent repetitions we will call the first substance, precipitate A, and the second, precipitate B. A substance that includes both A and B is obtained when acid is added to the urine in the first instance. This we will call precipitate C. When precipitate A is absent, precipitates B and C are, of course, identical.

This latter substance, precipitate C, was recognized by a Hungarian chemist, Paul Plosz, and described by him in 1890 in an article in a journal published in the Hungarian language at Buda-Pesth. A review of this article by Liebermann is to be found in Maley's *Jahresbericht der thierischen Chemie* for 1891.

Plosz enters quite fully into the chemistry of this substance, which he finds to be a form of albumin. He declares that it is present in every urine, a statement which I believe to be incorrect, as I have several times failed to obtain it. He does not seem to be aware that a precipitate can be obtained without the intervention of an acid, nor that the precipitate of which he speaks is made up of two distinct substances, easily separated the one from the other. He says nothing in relation to the physiological or clinical significance of the reaction.

With the exception of this article by Plosz, I have not been able to find any reference in medical literature to the subject of this paper.

If absolute alcohol be added to any of the gelatinous substances A, B, or C, a dense, white, opaque coagulum is formed resembling coagulated albumin. This is more or less soluble in acetic acid, and the solution responds to the potassium ferrocyanide test, showing that we have a proteid body. The coagulum obtained from "A" is, however, more soluble in acetic acid than that from "B." Still, different specimens of urine will yield somewhat different results in all these particulars, showing that neither A nor B has a definite composition, but both are subject to slight variations due, probably, to differences in diet, hygienic conditions, etc.

We have, then, in nearly every specimen of normal urine a substance or substances very closely allied to serum albumin—indeed, so closely allied that a very slight change may make them identical in some of their reactions. It seems, therefore, that we should be wary in accepting the results of new and so-called "delicate" tests for albumin. Any combination, for example, of an acid with an alcohol by which an ether should be generated, might, very possibly, give a precipitate in a perfectly normal urine.

In regard to the physiological and clinical relations of this test, precipitate "A" is found in nearly every specimen of normal urine taken within twelve hour after an ordinary meal. It is frequently

absent in the morning urine, especially if the bladder has been already emptied during the night.

It is usually absent when the diet is greatly restricted, as in typhoid fever, nephritis, etc. It is rarely present when the patient is fed exclusively upon milk. It is absent, or present in very small amount, in infants and young children. It is often present in alkaline or neutral urine—indeed, it is only in such urine that the substance forming the typical precipitate "A" can be supposed to exist. When the urine is acid there is, probably in every case, an admixture of precipitate B.

In fact, the acid spontaneously formed in the urine by the acid fermentation will cause the ether reaction to take place in urine two or three days old, when the same specimen, tested immediately after it was drawn failed to give the slightest response. In such cases we are in reality dealing with precipitate B, instead of precipitate "A." When present the bulk and density of the precipitate seem to be proportionate to the vigor of the appetite and the completeness of digestion. In dyspeptics it is often scanty or entirely absent. It is strongly marked in the bracing air at the seaside; less so, in the same persons, under the depressing influences of town life.

Precipitate B is very rarely entirely absent, though it is often very small in amount, especially in very acid urine. It may, however, be abundant when precipitate "A" is scarcely obtainable. Still, in a general way, the circumstances which determine the amount of one have a similar influence upon the other.

As to the nature of this substance, it has been suggested to me that it was mucin, derived from the mucous membrane of the genito-urinary tract. But the reaction is just as marked in urine from which the mucin has been removed by boiling with acetic acid.

I may remark in passing that this substance is precipitated also by chloroform, with which it forms a dense, white emulsion. That it is the same substance appears from the fact that urine which has been thoroughly exhausted with ether will not yield this emulsion.

It is interesting to observe that a cold infusion of muscle of beef, from which infusion the albumin has been removed by boiling, will give a precipitate with ether, apparently identical with that from urine. The same is true of the white of egg, and of a watery solution of dried serum albumin.

Albuminous urine behaves, in regard to this test, in no way differently from normal urine when ether alone is employed. But the addition of acetic acid produces an amount of the precipitate which far exceeds the product from normal urine. That this excess is derived from the albumin is shown by the fact that, when the albumin is first removed by boiling, the addition of acetic acid results in only a moderate increase of the precipitate as compared with that obtained with ether alone.

Other acids produce the same effect upon albumin, viz.: to make it precipitable by ether. Even nitric acid, while it precipitates the albumin, re-dissolves some of it, and this solution responds readily to the ether test. If, for example, we take urine from a case of Bright's disease, boil it, filter out the precipitate, wash it with distilled water, and then drop upon the filter a little nitric acid, we shall find that the water used for subsequent washings will give the characteristic reaction with ether.

The presence of sugar in the urine does not seem to modify the reaction in any way. I have here a specimen of urine from a patient passing about 900 grains of sugar per day. She is upon diabetic diet not rigidly enforced. Precipitate A is seen to be very slight in amount, while precipitate C, obtained in this case by adding phosphoric acid, is decidedly abundant. This urine contains no albumin.

Peptone in the urine gives a rather decided reaction.

There is one circumstance connected with this reaction which may prove to be important. It is well known that after prolonged etherization, anuria occasionally occurs and may prove fatal. Though not confined to patients having albuminuria this accident is most frequently observed in connection with that condition. We have seen that albumin in an acid urine increases very greatly the amount and density of precipitate B. At the same time we know that ether, when inhaled, is eliminated partly by the kidneys, as its odor is readily detected in the urine. Now the urine and the ether being distilled together, as it were, into the tubules, the most intimate mixture of the two is assured, and the conditions are eminently favorable for the formation of a gelatinous precipitate, which would effectually plug the tubes and arrest the function of the kidney. Just this condition has been found in a case of this kind reported by Dr. W. H. Porter. But it is not necessary that the kidneys should be

diseased, or the urine albuminous, in order that this result may be produced.

As we have already seen how dense a precipitate may be formed in urine that does not respond to the test for albumin, all that is required is that there should be a large proportion of nutritive material in the blood, and that the urine should be decidedly acid.

Should further experience confirm this hypothesis as to the mechanism of the anuria in these cases, it would suggest that preparation for an operation in which ether is to be used should include a period of low diet and the production of an alkaline reaction in the urine.

In conclusion, the reaction of ether with urine presents a field for study which may lead to important results. It appears to afford, in some degree, an index of the readiness with which digestion is performed and the products of digestion taken into the blood. It may hereafter be found to be quite as important to know how much unused material is voided through the kidneys as to appreciate the amount of disintegrated tissue that is represented in the urine.

The influence of different kinds of food, of different habits of life, and of different physiological and pathological conditions are so many points yet to be worked out.

Again, may not some relation be found to exist between the labor thrown upon the kidneys in the excretion of this material and the ultimate production of renal disease?

And still again, when the kidneys are diseased and the urine charged with albumin, may not the obstruction in the tubules be increased by the use of ethereal preparations as medicines, the urine being at the same time acid?

Finally, it would be interesting to ascertain to what extent, if at all, the toxic properties of the urine depend upon the substances in question.

PROBABLE ORIGIN AND EARLY SYMPTOMS OF CERTAIN CHRONIC DISEASES OF THE KIDNEYS.

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On entering the discussion of this subject it may be taken for granted that no chronic disease of the kidney with a definitely known origin will be considered, except, incidentally, it may be to reinforce arguments tending to establish the obscure cause or causes of the more numerous classes of these diseases. Chronic diffuse nephritis, having for its origin diphtheria, scarlet fever, or pregnancy, although little is known concerning the action of these causes, is not to be considered in this paper. The same may be said of suppurative nephritis, cancer of the kidney, pyelo-nephritis, embolism, or thrombosis, tubercular nephritis, tumors, or renal calculi, hydronephrosis, and cystic conditions of kidneys, since these pathological changes are also referable to causes, many of which are still unknown, yet differing so widely from the probable ones under discussion as to make it necessary to eliminate them.

It will be the endeavor, therefore, to seek as far as possible the ultimate cause or causes of those chronic changes found, for the want of more specific knowledge, under the ambiguous head of chronic Bright's disease. The post-mortem appearances of these kidneys have so many points in common, that, without intending to disregard the often useful classifications of these lesions, it will be much more convenient to consider them under one head, as the differences are due largely to the extent of the irritation on a more or less unstable tissue, rather than any marked, uniform pathological appearances.

The cases of chronic congestion and degeneration present well-marked, widely differing conditions, both as compared with each other as well as with the more numerous classes of Bright's disease; but

as these changes are incident to mechanical interference with the blood-current, or to other well-known causes, as the excessive use of alcohol, it would be of no value to mention them, but for the fact that the appearances of the dominant classes are modified by these collateral causes, and to this extent mar the perfect type of the diffuse varieties, thus, no doubt, adding something to the necessity of using the terms, "with or without exudation."

Aside from these considerations, we find in chronic Bright's disease a minimum or a maximum quantity of exudation from the blood-vessels, in the tubules or in the urine. The renal epithelium is degenerated; the stroma has developed a new connective tissue; the capillaries, by waxy degeneration or otherwise, are obliterated in various regions of the kidney, while the walls of the arteries are irregularly thickened or closed. According to the amount of congestion, there is connective-tissue development or obstruction of vessels; the kidneys are of larger or smaller size as a whole, or in many local foci given either a nodular or large smooth surface. The element of time that must be added to these post-mortem appearances determines the extensiveness and completeness of these destructive changes. The term *diffuse* expresses the accepted knowledge of the general character of these lesions, and if we take in consideration with this the difference in tissue composing the various parts of the kidney, together with the degrees of unequal nervous tension that control these tissues, we may predicate a few agents as causative factors in these diseases.

If a post-mortem be held on individuals dying from other causes during the early stages of Bright's disease, the same diffuse character of these initial steps may generally be demonstrated; and while it cannot be affirmed that, without exception, these diseases have their origin in this general way, still the weight of evidence points very strongly in that direction. Again, if our post-mortem research be extended to the bloodvessels, capillaries, and heart, the general character of these diseases becomes more and more apparent, and consequently we are made grateful for the admirable work of Gull and Sutton, Johnson and Arthur Meigs, who have convinced us of the importance of noting changes in these blood-conveying channels, which are prominent factors not only in the kidney lesions but also furnish a more definite knowledge concerning the initial steps producing these widely distributed results.

Without entering into the merits of the brilliant discussion which took place a few years ago among the gentlemen named, it will only be pertinent to this paper to point to the general tendencies developed by such knowledge. It matters not, therefore, whether the intima of the bloodvessels is diseased—as shown by vast areas of irregular thickening in their walls—whether the capillaries are also involved in extensive fibrosis, whether the muscular tissue is primarily or secondarily involved, or whether, according to DaCosta and Longstreth, there is a constant lesion of the renal nerve plexus, or other ganglia, remotely producing phenomena acting in concert, the argument from one and all of these, if demonstrated to be true, would be in harmony with the view that the irritant, or irritants producing these lesions are presented to these various tissues in more or less constant quantities through the blood-current itself. That a tissue or nerve plexus should be more affected than the same kind of tissue or ganglion in remote or contiguous parts of the body, under the same cause, is only the iteration of an old truth, the knowledge of which is patent to all, but the explanation is vastly more obscure. It is not the purpose, therefore, of this paper to try to harmonize the different views advanced by these authors, or to labor vainly to explain the reason for the remote lesions in the arteries of the head, trunk, and extremities, that exemplify the existence of a common origin, but only to note in passing the importance of the relation of cause and effect, that is thus by hypothesis established. It is granted by most authors that alcohol, for example, when taken into the circulation in large quantities for a long period of time, has the power to thus change the character of tissue, causing a cirrhosis of the liver, a fibrosis of bloodvessels, and is mentioned as a prominent factor in the causation of certain forms of Bright's disease. In these cases a general irritant affects unequally the various tissues with which it comes in contact, combining with one in the first individual and with another in the second, and not seeming to affect severely the third in any region. It, therefore, appears that the integrity or resistance of the tissues, together with the irritant, determines the place and extent of such lesions.

If we now turn from the dead to the living subject, we find abundant evidence of the general character of these changes. In the late stages of the disease we find hypertrophy of the left ventricle,

with or without lesions of the mitral valves, accompanied by the hard, resistant pulse, indicating high arterial tension; the congested mucous membranes, with occasional hemorrhage from them; the dyspnœa, headache, and œdema, that show an increased blood-pressure; the tendency in many instances to inflammations of serous membranes, in often remote parts of the body; the cirrhotic and waxy degenerations, indicating both the altered blood-tension and a more or less constant irritant; the apoplexies, in the course of these symptoms, with abundant evidence of kidney lesions; the purpuric extravasations; the inflammatory skin diseases that often precede for a long period of time the more serious lesions now under discussion, show also how widely distributed are these consequences.

Nor are the earlier stages of vessel lesions any the less marked. Before albumin and casts are found in the urine—if the case finally lapses into that condition—many of these symptoms are present; but in repose are often not so pronounced. The least exertion, as walking rapidly for a few steps, or climbing up a flight of stairs, or exercising the arms, as in sweeping, or lying down, or getting up suddenly, will demonstrate at once the condition of the circulation. Not only will the volume of the pulse be increased, but the rate will not be commensurate with the exercise performed. Irregularity of the pulse is at these times also well-marked, whereas, in times of quiet, the pulse resumes its normal regularity and compressibility. At other times, such patients, during these early stages, are inclined to palpitation of the heart, a symptom often deserving more consideration than it receives. It may be a fact that palpitation results frequently from reflexes, due to irritation in remote regions of the body, and many of these may, with some semblance of truth, be attributed to stages of indigestion; but it is to be doubted in the cases under discussion whether any such cause can be held responsible for the constant reappearance of these "fluttering" hearts, unless—as is probable—this condition is a common factor resulting from products taken up from vicious digestion. It is more probable that the paroxysms observed in the early stages of these diseases are due to spasms of the small arterioles, thus bringing for the time additional work on the heart. The reasons for believing so are founded on the fact that such spasms are common to other muscular tissues, and are very pronounced in certain muscles in the middle and last stages of these diseases. Again,

it is a frequent observation that these so-called palpitations are gradually submerged into the more or less constant irregularity of the heart's action, and finally are accompanied with dyspnœa and other marked characteristics of these diseases. It will be seen, therefore, from this standpoint, that it is an easy task to harmonize the arguments before cited concerning ganglia, the intima, or muscular tissue-changes, which have primarily or secondarily an importance in the course of these lesions, since they are all probably the result of the more remote cause, which in the blood of such patients is more or less constantly associated thus with them. If either albumin or casts are now found in the urine, the clinical evidence has reached that appalling stage of development which for many months has been foreshadowed by the numerous symptoms already referred to, and our patient is well on the road that finally leads to his death. Albumin and casts, therefore, only announce that these general tissue-changes have at last so involved the kidneys that such albuminous transudations were made possible; that the integrity of the organ had so far lost its resistance to the blood-current, that the normal osmosis has been converted into a transudation; the kidneys thereby losing a part of their normal function, to that extent, of selecting the end-products of the life processes from the blood. The specific gravity of the urine in consequence is lowered commensurately with the wastes if the amount of urine remain constant; but that the amount of urine is also often very much restricted, is still an additional argument in favor of very destructive tissue-changes in these organs. A knowledge of all or any of these products is of very little, if any, value in determining the primary cause or causes of this long trend of symptoms. And, indeed, it might with equal propriety be affirmed that the clinical value accruing from albumin casts and specific gravity of the urine is of little importance, since we have so many symptoms pointing to the existence of the general lesions long before these symptoms make their appearance, so that it is often a reckless waste of time to wait for these products in order to try to avert the final manifestations of the late course of the disease.

It is the experience of careful observers in this field that certain diseases, viz., rheumatism, gout, diabetes, and less frequently other morbid conditions having a wide area of distribution, are often interchangeable as causative agents in the production of their characteristic

pathological sequences. For example, rheumatism is frequently associated with some of the early and late manifestations of chronic Bright's disease. It also has a close relation to the clinical manifestations of gout, while a so-called rheumatic inflammation is not unfrequently associated with diabetes. Again, diabetes and gout are often closely allied with Bright's disease, while at the same time there is established an intimacy between the diseases themselves. Certain severe inflammations producing materies morbi, having the blood as a conduit, also produce similar changes, such as the articular inflammations following septicæmia, or pyæmia in a less marked way, also in the so-called gonorrhœal rheumatism.

What do we learn, *a priori*, from these facts concerning the cause of chronic Bright's disease? If an excess of uric acid in the blood will produce an irritation in certain susceptible tissues of the joints, sufficient to cause permanent concretions in these joints, from malassimilation, it is not a fallacious argument to infer that other tissue sensitive to such poison would, in the degree of that sensitiveness, be also affected and form products common to such tissue. It would, therefore, take no flight of imagination to predicate such changes in many regions of the body: atheroma in arteries and congestion of kidneys, if not an actual chronic inflammation in some instances. That uric acid is not the sole or even frequent cause of Bright's disease, clinical experience affirms; still, that it even occasionally is so associated with this disease proves the potency of such an irritant, and adds that much to the developing evidence that the kidney inflammation is due to irritants found in the blood. If lactic or other acid should ever be demonstrated to bear a causative relation to rheumatism, it would also prove that through its chemical composition it produces in joints and other tissues with which it comes in contact in the blood—as might be predicated—a degree of such irritation by vicious chemical unions with the compounds composing such tissue, and that it has less or no influence on some regions would only demonstrate the want of chemical affinity or invulnerability of such tissues to this compound. The argument from these and kindred diseases is, therefore, that since there is no constant relation existing between them, the causes which produce them are different, at least in the more numerous instances. That this correlation is only established in the case of gout and Bright's disease, and that each of these

diseases has occurred without the other, makes it apparent that even they must often at least have two sources of origin. Uric acid, then, may be put in the list as an occasional cause of Bright's disease. But what causes such an increased quantity of uric acid? There is an intimate relation existing between this compound and urea. It is probably a matter of oxidization to determine the quantity of the one or the other product, as it results originally from the nuclein of the cell. To say, therefore, that this relation of about 1 to 50 in health is disturbed is to introduce at once a more powerful factor into the causation of even this intermediate cause of Bright's disease.

For many years it has been the observation of all students of this subject that the retained products of excretion, of whatever character produced evidence of more or less extensive irritation, which, if continued, invariably led to the death of the individual. Uræmia, whether it be caused from urea, ammonium carbonate, creatine, creatinine, or other constituents of the urine, is so intimately associated with the retention of the nitrogenous products as to be entitled to that consideration. It is a fact, also, that in the early stages of Bright's disease the average daily quantity of nitrogenous products excreted is very much diminished. This would show that either these products were retained or that the normal changes incident to their production had been interfered with. The reason for believing that they are not excreted is shown from the observed uræmias that occur often, even in the early course of these lesions. It is very probable, therefore, that this dominant nitrogenous product of the living processes of the body, in some mediate or intermediate way, also acts as a causative agent in the production of those numerous changes now known to constitute the roll of Bright's disease; but, as in the case of uric acid, a preceding cause must exist that prevents its excretion or its formation, as both of these functions are normal processes, and therefore by the inertia of such forces should continue —unless disturbed—their proper action.

It is an observation which has been made by many authors, that Bright's disease is frequently incident to the processes of growing old. If the evidence of cell segmentation to make new growths in blood-vessels, kidneys, and heart is a normal condition, it would be better to relegate this to the exuberance of more youthful subjects. Ac-

cording to the tables at command, the age of fifty marks the largest number of these cases. At fifty, therefore, we should expect to be on neutral ground, as between youth and old age, and consequently, if at any age immunity could be attained, it would be at this. That even at the advanced years of seventy or eighty an irritation could induce such stable tissue to an atheromatous inflammation by an increase over often large areas of endothelial cells, is a strong argument in favor of a most powerful extrinsic cause. We have abundant evidence in many parts of the body of such irritation. The changes in the retina in the early stages, the inflammatory conditions of the skin, the increased nervous excitability causing insomnia, neuritis, and neuralgias, are examples of very early evidence of the presence of the irritant or irritants producing these changes. A long time before albumin and casts are found in the urine, while the patient is in comparative health, the weight may suddenly increase many pounds, and the dyspnœa that comes later, on slight exertion, be attributed to this cause. Such changes may occur at all ages, and mark the beginning of these diseases. Now, fortunately, we have many analogies among chronic diseases to support the correctness of these views. As in the case of diabetes and alcoholism, for example, patients, after the first stimulating effect of the irritants has worn away, and the tissues have become burdened with the more or less constant presence of these substances, while the normal force of the cell is expended in the direction of new growth, on a vitiated blood, with consequent organic disease, loose tissue in other regions of the body, and emaciation marks the declining years of life. It is not intended to claim that this is the rule in the early stages of Bright's disease, but such cases are numerous enough to serve as examples in this connection. Nor is it intended to open the discussion again of arterial fibrosis, but to call attention to clinical evidence of disease that the after-history shows is intimately associated with such lesions.

The almost uniform symptom that is present in the very earliest manifestations of those changes incident to these diseased conditions is one referable to the stomach and bowels of such patients, a chronic gastritis seeming to be often the initial lesion. It would be quite an impossible task to undertake to review the late knowledge bearing on these primary steps, and I shall not burden the paper with other than a very brief reference to the causes which are now known, from

vicious changes in stomach and bowels, to be factors in the causation of mal-assimilation, and thus disturb the proper metabolism of cells. A great number of chemical compounds may result from the many different foods under varying conditions of digestion in stomach and bowels. And when we add to these, changes wholly or in part occurring outside of the body, together with the bacterial products in these digestive organs, such a mass of organic and inorganic chemicals are collected as is seldom found in such narrow bounds. What wonder, therefore, that vicious unions are often found that not only irritate the walls of the stomach and bowels, causing acute and chronic inflammations, but are also absorbed and pass into the general circulation, causing more or less continuous irritation to the various tissues of the body.

A number of poisons have the power, when injected into the blood-current, or when reaching it by the natural channels of absorption, of producing very serious inflammatory states in not only the tissues of the kidneys, but of the endothelium of bloodvessels in remote parts of the body, thereby causing many of the symptoms of the diseases under discussion. The much-studied cantharidin nephritis will, perhaps, serve best as an example of this class of extraneous substances which, thrown into the blood, cause in the kidneys an acute Bright's disease. However interesting this class of drugs may be from an etiological standpoint, for the purpose at hand it does no more than to demonstrate the immediate power of extremely irritating substances, which, no doubt, act directly on the tissues with which they come in contact, and act most upon the vessels of the kidneys because most intimately associated with them. The most interesting field now under observation is that of chemicals produced as end-products in the life of certain bacteria, in the alimentary canal, or in substances outside of the body, but which find their way finally into this channel. The ptomaines are, many of them, known to be poisonous, and, in consequence of making chemical unions with various tissues, cause or contribute to the production of several well-known pathological lesions.

Without going into a discussion of these numerous ptomaines, with which you are no doubt familiar, it will not be too far from the truth to assume that some of these poisons, also, are carried at frequent intervals, in persons having chronic gastritis or other gastro-intestinal

lesions, into the blood, causing irritations and thus also disturbing the proper metabolism of cell-life. The lassitude following a heavy meal, insomnia, serous inflammation, mucous irritation, convulsions, neurasthenia, and many other kindred diseases are attributed to such chemical agents by some authors.

Again, the equilibrium of the normal cell functions may be disturbed by the surface of the body being lowered in temperature suddenly, thus causing the formation of leucomaines that make vicious chemical unions in the interior of the body with serous and mucous membrane irritations, and primarily or secondarily involving the excreting organs. Many other extrinsic causes might thus be named that are, no doubt, factors in disturbing the normal metabolism of the cell, and account for the unequal distribution of these lesions as to climate.

The causes, therefore, that primarily produce the irritants, secondarily causing that long trend of pathological changes so indissolubly associated with Bright's disease, are those agents that disturb the metabolism of the cells of the body, causing them to run down outside of their lines of normal cleavage, in their life manifestations, and thereby producing an excess or diminution of products, normal and abnormal, to the blood. In this metamorphosis, no doubt many products will yet be found that are not now known to bear any relation to these lesions, and many others are now found in the urine which will be demonstrated to be due to cell disturbance in the otherwise diseased kidney that are abnormal expressions of such cells and that have nothing in common with the original causes of the vessel and kidney lesions. There are many of the primary irritants, only a few of which has time permitted to mention. Some of these affect, from their chemical composition, one class of cells more than others, thus marking the seat of greatest change in tissue.

As would be expected from this line of argument, the normal end-products of metabolism are the first indices of the departure from such norm, and an accurate knowledge of these compounds will furnish the first definite information concerning the varied lesions now known to constitute Bright's disease. A thorough knowledge of the nitrogenous compounds for a long period of time, from known quantities of urine during twenty-four hours, will furnish a differential diagnosis between primary causes as cited and the results of

consequent tissue-changes in the various cells of the body. Such a knowledge is of prime importance not only to foresee the trend of the ultimate outcome of such conditions, but is of great value in reckoning the rate the disease is progressing. After a disturbance is discovered in the constant average excretion of the dominant compound urea for several weeks, on a mixed diet and in an otherwise healthy person, the evidence is present that marks the earliest clinical knowledge of what probably is the beginning of the second stage of these changes. The symptoms belonging to this stage, as before described, will now make their appearance, and whether Bright would recognize these initial steps, having so many possible consequences, the presumption remains that it is through them that the kidneys are finally caused to present his well-marked pathological appearances.

As this paper is already much too long, I shall not burden you further with an intended synopsis of one hundred cases which have been under observation from two to eight years, but will simply refer you to fifty cases in the *American Journal of the Medical Sciences*, January, 1890, that exemplify these statements, and state that the remaining fifty cases now on my records show with equal emphasis the truth of former statements.

DISCUSSION.

DR. WHITTAKER: I have listened with great pleasure to this paper by Dr. Bond, but I am sorry to say that I fail to be convinced by the array of symptoms which he presents that he has described the earliest symptoms of Bright's disease. It is desirable that we should recognize Bright's disease earlier, but I feel sure that most of us would fail to believe that the prodromata that he mentions are always indicative of commencing nephritis. We will find such symptoms as dyspnœa, erethismus cordis, excitability of the nervous system, neuralgia, etc., as prodromata of many different diseases. We see these symptoms in the initial stage of typhoid fever and in the preliminary stages of tuberculosis. I do not believe that it is fair to assume that Bright's disease will develop because of the presence of these symptoms for weeks or months before signs in the kidney show themselves, neither can the amount of urea predetermine this fact. We have not come to the time when examination of the urine is rendered superfluous by these prodromata.

DR. BOND: Dr. Whittaker has misunderstood the province of the paper if he understood me to say that the examination of the urine was not a necessary thing, as I have distinctly stated in my paper that critical examination of the urine is of very great importance. In typhoid fever, for instance, we would not find the conditions present in the urine that are found in the cases cited in the paper, as in typhoid the amount of nitrogenous products is very great, and is constantly so.

A STUDY OF ADDISON'S DISEASE AND OF THE ADRENALS.

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SINCE the description was published by Addison, in 1855, of the disease which bears his name, much study has been expended upon the etiology of this remarkable affection. The present research has been undertaken with the view of formulating such conclusions in regard to the etiology and symptomatology of Addison's disease as our still limited knowledge of the subject justifies. My personal experience includes three cases with autopsies, and to these are added three more, which are all that careful search discovered among the statistics for the past ten years of the New York and Presbyterian Hospitals. In addition, I have collected unreported records of 40 autopsies in which lesions of the adrenals have been noted, but without accompanying symptoms of Addison's disease.

In two exhaustive articles by Lewin (*Charité Annalen*, 1885, p. 630; 1892, p. 536), all cases of Addison's disease and of diseases of the adrenals which were reported prior to the latter part of 1891, were tabulated to the number of 684. I have brought this work up to date, analyzing 73 more histories. This total of 757 cases, recorded by many different observers, constitutes a series large enough to afford definite data, since autopsies were made in nearly all.

The term "Addison's Disease" strictly applies to an affection which, as described by Addison himself (Dr. Addison's Works, New Sydenham Soc., 1868, p. 211), includes, among less characteristic features, extensive bronzing of the skin; but since in many instances the pigmentation is absent, while the other symptoms are decided, and are accompanied by the lesions common to the typical form, conclusions will be drawn from both classes.

The six new cases are here annexed. All were characterized by very decided bronzing of the surface of the entire body, which in one instance only was accentuated here and there by oval spots of a blacker hue. In addition, all the patients presented a group of definite symptoms, viz., great muscular weakness and prostration, indistinct heart-sounds, feeble pulse, pronounced gastric irritation with repeated attacks of nausea and of almost uncontrollable vomiting, mental apathy, and local pain.

In three of the cases in which autopsies were obtained, both adrenals were found softened and degenerated to a degree which entirely obliterated their original structure.

The first of the cases which came under my care was so unusual that it deserves special mention.

CASES OF ADDISON'S DISEASE PREVIOUSLY UNREPORTED.

CASE I.—The patient, J. A., was an intelligent Irishman, fifty years of age. He was admitted to the Presbyterian Hospital on May 5, 1891. He contracted syphilis several years before, and also suffered from frequent severe attacks of malarial fever during a three years' residence in Central America. Eight months before admission he noticed discoloration of the skin, general muscular weakness, and indigestion, especially of fatty food He also had more or less diarrhœa, and for two months he suffered greatly from nausea and vomiting. On three occasions he was seized with sudden faintness, accompanied by severe pain in the right hypochondriac region. Five months before admission his skin began to darken and became more and more bronzed. The color appeared first upon the face and later upon the trunk and extremities. The intensity of the discoloration varied from time to time, but on the whole progressed quite rapidly.

On admission the chief complaint was of general muscular weakness. Physical examination of the lungs and abdominal viscera revealed nothing abnormal. Heart-sounds extremely feeble, pulse feeble, soft, compressible, 72. Respiration and temperature normal. Urine normal. Red blood-cells 1,922,000 per cubic millimetre. Body ill-nourished, but not emaciated. The face and hands were of a dull mahogany-brown color, the rest of the integument of a lighter brown.

After several days of rest and tonic treatment the patient gained in strength and was allowed to go out for exercise. After some hours he returned very hungry, and said that he had been evicted from three restaurants where he applied for lunch, on the ground that he appeared to be a negro, which indeed he resembled. (I exhibit a fac-simile of the color of the face and chest.) After this experience he remained in the hospital, and became progressively weaker and mentally dull, with a rapid and extremely feeble pulse. He also had another seizure of pain in the right hypochondrium, which was

very intense and followed an evacuation of the bowels. The visible mucous membranes became pigmented.

The man suddenly developed pneumonia and died on the thirteenth day.

The *autopsy* showed both the adrenals to be normal. The liver exhibited syphilitic cirrhosis. The splenic capsule was thickened and adherent, and the spleen itself was soft. There was some thickening of the duodenal mucous membrane. Pneumonia was present at the base of the right lung. Nothing else of importance was observed.

CASE II.—S. H., male, thirty years old, German. Admitted to Presbyterian Hospital. No history of alcoholism or of syphilitic infection. Excepting several attacks of malarial fever, general health good until two years ago, since which time there have been frequent attacks of nausea and vomiting, with severe headache and anorexia. For the few weeks prior to admission, great languor and muscular weakness with increasing gastric distress and vomiting were present. Patient vomited constantly for three days, and complained of fever and a sore throat.

Examination on admission. Anæmia decided, emaciation extreme. The entire surface of the body, and especially the skin over the chest, scrotum, and thighs is of a dusky brown color. The hue presents a uniform gradation from that of a light mulatto on the chest to that of a dark negro in the above situations. No isolated patches of pigment, no icterus, conjunctivæ normal, no discoloration of the buccal mucous membrane. Acute catarrhal tonsillitis is present. The heart-sounds are feeble, and a pulmonic anæmic bruit is heard. The free border of the liver extends to the umbilical line. Spleen moderately enlarged. Urine contains albumin with hyaline and granular casts. Temperature 100°. Pulse 92.

The patient continued to vomit, the heart action failed, pulmonary œdema ensued, and delirium was succeeded by drowsiness, coma, and death. The urine was retained for twenty hours before death, and the final temperature reached 105°.

Autopsy. Heart-muscle soft, valves normal. Lungs normal. Liver enlarged, cirrhotic, mottled with hemorrhagic spots. Kidneys in condition of acute parenchymatous nephritis. *Adrenals:* both enlarged and completely degenerated, filled with caseous débris, no gland-structures remaining. Semilunar plexus and adjacent sympathetic nerves appear normal. Spleen double the normal size, dark, soft, pultaceous.

CASE III.—H. W., male, forty-four years old, Englishman, waiter. Admitted to the Presbyterian Hospital. Previous history of moderate drinking, attacks of malarial fever, rheumatism, and syphilis. Since having rheumatism, four years ago, the patient has had occasional œdema of the lower extremities and moderate dyspnœa upon exertion. Nine weeks previous to admission he began to suffer from anorexia, nausea, and vomiting, and lost strength and flesh. One week before admission he was seized with severe pain at the base and left side of the chest, which was followed by a chill the next day. He also complained of a painful dry cough.

Examination on admission. General nutrition good. Entire surface of body moderately pigmented, darkest on hands, face, and genitalia. Hue that of a light mulatto. No patches of pigment. No pigmentation of visible mucous membranes. Pulse very feeble, 100. No cardiac bruit. Temperature 101°. Dry pleurisy at base of left side of chest. Liver-dulness diminished in area. Splenic dulness increased. Urine normal. On the third day effusion appeared in the left pleural sac, the heart-action became extremely feeble, and uncontrollable nausea with vomiting and distressing singultus ensued. Both stomach and rectum rejected all food. On the eighth day a general convulsion and pulmonary œdema occurred, and the patient died in coma.

Autopsy. Besides the fluid in the left pleural sac, large lipomatous growths were found projecting from the pleural surface of the diaphragm on the left side, in masses resembling a cock's-comb, which were 1½ to 2 inches long, and could be readily stripped off. Lungs œdematous, otherwise normal. Heart covered by a large layer of fat, valves normal, walls very soft. Liver small and slightly cirrhotic. Spleen enlarged by one-half and deeply pigmented. Kidneys surrounded by fat. They show early stage of chronic diffuse nephritis. *Adrenals:* each as large as a hen's egg, cortex completely caseous, medulla somewhat softer, but without pus. Not a trace of original structure remains. Both surrounded by large accumulations of fat. No abnormality of semilunar ganglia observed.

CASE IV.—S. M. H., female, fifty-seven years old. Twenty months before her death, while in apparent good health, patient observed dark brown spots which first appeared on neck, then on thighs and hands Since then bronzing has become diffuse, and the patient has had occasional attacks of anorexia, nausea, vomiting, and prostration. She was twice admitted to the New York Hospital, with a year's interval. The first time that she entered the hospital her symptoms were mainly nausea, vomiting, epistaxis, insomnia, and muscular weakness, with moderate bronzing. After a few days the patient was discharged improved. Five weeks before admission for the second time, patient had severe vomiting, headache, constant pain in left hypochondrium, followed by rapid loss of flesh and strength. Has at times passed almost no urine, at other times has had moderate polyuria. Frequent epistaxis occurred.

On admission the integument was found deeply bronzed over the entire body, but especially so where exposed to the air. Conjunctivæ not pigmented, but lips and buccal mucous membrane spotted with dark gray patches. Anæmia was observed, with marked asthenia, mental hebetude and despondency, and the pulse was weak, small, and compressible. The patient died quite suddenly the same day of asthenia.

Autopsy. Body fairly nourished, rigor mortis well marked. Entire body distinctly bronzed with the exception of an old cicatrix 1½ inches in diameter in centre of forehead. Peritoneum, showing adhesions between liver and other viscera, and about the spleen. Heart brown, size and valves normal. Lungs, spleen, stomach, and intestines all normal. Liver small, cirrhotic, and

pigmented. Brain and its membranes normal. Kidneys small, with adherent capsules and a few superficial cysts; cortex thin and markings indistinct. *Adrenals:* normal in size but irregular in thickness and nodular; cortex and medulla not distinguishable, studded with small caseous masses. Microscopic examination shows many small caseous areas surrounded by masses of young cells with numerous giant-cells among them. No trace of original structure of medulla or cortex.

(The two following histories are incomplete in that they are without autopsies, but they illustrate the correlation of the symptoms of asthenia, pigmentation, vomiting, feeble pulse, etc.)

CASE V.—J. P., male, twenty-two years old, waiter, Englishman. Ill but two weeks with great muscular weakness and mental apathy. On admission to the New York Hospital the patient's condition was as follows: general nutrition good; no visceral lesion discoverable on physical examination, but the urine contains granular and hyaline casts. Blood examined and found normal. There was decided bronzing of a large surface of the body, especially over the chest and abdomen. The nipples were quite black. The patient appeared in a condition of melancholia, obeying when directed, but refusing to speak, and he would not voluntarily move or change his expression. Emaciation soon followed and became extreme.

After six weeks of treatment the mental condition failed to improve, and the patient was transferred to another institution.

(For the privilege of abstracting the two previous histories I am indebted to Dr. Peabody, in whose hospital service they occurred.)

CASE VI.—E. T., female, forty-six years old, laundress, Irish. History of occasional attacks of rheumatism and malarial fever. For 1½ years prior to admission to the New York Hospital and following exposure to cold and wet, the patient had occasional attacks of intense pains in the back and hips, vertigo, headache, and severe vomiting. On admission complained of shortness of breath, nausea, vomiting, and asthenia. Patient has noticed great variations in the quantity of urine at various times. Bowels constipated. For a year patient's skin has been growing uniformly dark, with brown spots on hands and body. Physical examination failed to reveal any visceral lesion. General nutrition good. Heart sounds very feeble; valve sounds normal; pulse 98, weak. Entire surface of body dark brown, inclining to black in certain regions. On the hands, feet, and body there were a few oval spots of darker hue than the surrounding skin. After some days of treatment the patient was discharged somewhat improved.

LESIONS OF THE ADRENALS.

Disease of the adrenals occurring as the sole lesion observed of any importance, is recorded in nearly one-half of all cases, while in a

further large number it accompanies or is secondary to lesions elsewhere. But we are obliged to abandon the earlier theory that Addison's disease is etiologically dependent upon adrenal lesion, in view of the fact that many typical cases have lately been observed such as one just cited (Case I.), with well-marked bronzing, in which the adrenal bodies were entirely normal. Among Lewin's histories 12 per cent. were of this type. Virchow describes a typical case with pigmentation, in which the microscopic examination of both the adrenals and sympathetic system presented nothing abnormal. Moreover, it is well established that every variety of adrenal lesion which has ever been found associated with Addison's disease, has also occurred without giving rise to any symptoms whatever.

A most instructive case is related by Jürgens, where the pressure of a large aneurism caused atrophy and degeneration of the left splanchnic nerve with typical bronzing and other symptoms of Addison's disease, whereas the adrenals remained entirely normal.

In addition to the 40 cases of adrenal lesions which I have collected from hospital records, the existence of which gave rise to no symptoms of Addison's disease, are 72 others recently reported, making in all 112. Such cases must be common in the experience of anyone who is especially looking for them. The 40 unpublished notes are as follows:

CASES OF LESIONS OF THE ADRENALS UNACCOMPANIED BY BRONZING OR ANY OTHER SYMPTOMS OF ADDISON'S DISEASE.

A. *Lesions other than simple fatty infiltration.*

CASE I.—Pleurisy, with effusion; hydro-peritoneum. Liver mottled and congested. Left kidney slightly enlarged, pale, with thickened cortex. *Adrenals* normal in size, but cortex strongly pigmented (yellow).

CASE II.—Acute pleurisy, with effusion and ulcerative endocarditis. Liver infiltrated with fat; stomach mucous membrane dotted all over with a large number of petechial spots; kidneys showing diffuse nephritis. *Adrenals* softened at centre, normal in size.

CASE III.—Cardiac valvular lesions and fibrinous pleurisy. Liver, cirrhotic; capsule adherent to diaphragm. Kidneys: right waxy, left very large, filled with abscess cavities; left ureter obliterated and converted into dense connective tissue. *Adrenals* both enlarged, with areas of yellow softening in medulla, cortex thickened and yellow in patches.

CASE IV.—Incarcerated hernia; gangrene of thigh. *Adrenals:* both enlarged and the seat of numerous hemorrhages and spots of softening.

CASE V.—Pernicious anæmia. *Adrenals:* both enlarged and cystic.

CASE VI.—Pulmonary embolism; large carcinoma of right supra-renal (left normal). No pigmentation of skin.

CASE VII.—Carcinoma of stomach. Hemorrhage in right supra-renal capsule.

CASE VIII.—Interstitial nephritis. Supra-renals much atrophied.

CASE IX.—Chronic diffuse nephritis. *Adrenals:* both cortices fatty. Interior of right completely degenerated.

CASE X.—Lobar pneumonia; chronic diffuse nephritis. *Adrenals:* both cortices fatty; right also cystic.

CASE XI.—Tubercular osteitis. Acute general miliary tuberculosis. *Adrenals:* both markedly increased in size, and containing many small grayish degenerated tubercular nodules.

For the notes of Cases IV. to XI. and for most of the cases of fatty adrenals cited below, I am indebted to Dr. Farquhar Ferguson, Pathologist to the New York Hospital, and to his assistant, Dr. George P. Biggs.

The report of Cases XII. to XXV. have been kindly given me by Dr. John S. Thacher, with whose permission I present the following notes:

He says: "I have gone over the records of my autopsies at the Presbyterian Hospital, St. Luke's Hospital, and the State Emigrant Hospital. There are 971 of these in which the abdominal organs were examined. In most of them the condition of the adrenals was observed, and in the majority (575) it is found noted. In only 15 is it recorded as abnormal, certain variations in size, color, and consistence which are commonly met with not being classed as abnormal."

[One of these cases was genuine Addison's disease, and is referred to elsewhere; the remaining 14 are as follows:]

CASE XII.—April 12, 1889. Pulmonary tuberculosis, pneumothorax. Left adrenal contains a yellow nodule moderately firm. Right adrenal same, but contains nodule ¾ inch in diameter.

CASE XIII.—Feb. 15, 1890. Tuberculosis of genito-urinary tract, lungs, intestines, cerebellum, cord, and adrenal. Left adrenal almost entirely replaced by a cheesy mass. Right adrenal normal.

CASE XIV.—July 13, 1890. Cancer of cardiac end of stomach; cancer of mesenteric and retro-peritoneal glands and liver; chylous ascites. Left adrenal contains white carcinomatous nodules.

CASE XV.—Jan. 30, 1891. Fractured ribs; hemorrhage into pleura; acute pleurisy; hemorrhage into spleen; complete fracture of ulna. Left adrenal contains a nodule about one-third inch in diameter, rather soft in con-

sistence, pinkish-yellow in color. Right adrenal contains a nodule like the other, but flattened, with grayish color, and separating readily from the rest of the organ. Microscopic examination: cells fatty.

CASE XVI.—April 3, 1891. Chronic cystitis; chronic pyelo-nephritis. Right adrenal firm; on section found to contain a few pea-sized, firm, yellow masses. Left adrenal contains nodules like the right. Microscopic examination: typical tubercular inflammation.

CASE XVII.—Feb. 8, 1892. Grippe; facial erysipelas; pneumonia. Left adrenal extremely thin, gray, of normal consistence; right adrenal the same. Microscopic examination: many leucocytes in spots; new connective tissue in some parts. The adrenal cells are some of them proliferated, some of them degenerated.

CASE XVIII.—April 2, 1892. Cancer of œsophagus: gangrene of lungs; gastrotomy. Left adrenal contains a nodule one-half inch in diameter. Right adrenal, a similar nodule one inch in diameter. Microscopical examination: carcinoma, typical.

CASE XIX.—May 5, 1892. Chronic pulmonary phthisis. Left adrenal normal, except a pea-sized, yellow, caseous nodule.

CASE XX.—Sept. 2, 1891. Tubercular ulcers of intestines; perforation; peritonitis. Left adrenal, one end enlarged; on section shows a grayish, moderately firm mass three-quarters inch in diameter. Right adrenal the same. Microscopic examination: section consists almost wholly of small cells, little larger than leucocytes, mostly not round but pea-shaped and irregular, no alveoli; looks like sarcoma.

CASE XXI.—Jan. 25, 1893. Chronic tuberculosis of hip-joint; waxy degeneration of liver, spleen, and kidneys; broncho-pneumonia; acute pleurisy. Left adrenal appears normal. Microscopic examination: typical tuberculosis.

CASE XXII.—October, 1889. Cancer of lungs, heart, liver, kidneys, and adrenals. Latter contain small nodules one-quarter inch in diameter.

CASE XXIII.—Feb. 17, 1892. Paris-green poisoning; acute gastro-enteritis. Right adrenal contains a yellowish nodule about one-half inch in diameter, a little softer than the rest of the organ. Left adrenal normal. Microscopic examination: mass of adrenal cells in rather irregular alveoli, most of them in a state of marked fatty degeneration; a little infiltration of leucocytes at the periphery.

CASE XXIV.—March 26, 1892. Chronic nephritis: cirrhosis of liver; cardiac hypertrophy and dilatation. Right adrenal is replaced by a mass about twice the size of the normal organ, gray and granular. Left adrenal normal. Microscopic examination: typical tubercular inflammation.

CASE XXV.—April 21, 1893. Chronic cystitis; abscess of seminal vesicle; external urethrotomy; pyelo-nephritis; miliary tuberculosis of lungs. Both adrenals contain cheesy nodules. Microscopic examination: cheesy spots surrounded by infiltration of small cells and epithelioid cells; probably tubercular.

"I recall also two cases of diseased adrenal, not contained in the records mentioned. One was an employé at the State Emigrant

Hospital, who slowly and gradually became anæmic and asthenic, but no cause could be detected. His color was very white. After autopsy the adrenals were found cheesy.

"The other was a patient in the Colored Hospital. I can only recollect that at the autopsy the adrenals were cheesy and the tongue showed brown patches, and it was concluded that he had died from Addison's disease." (Thacher.)

The following case (XXVI.), as well case XL., was kindly examined for me by Dr. Warren Coleman, Instructor in Pathology, Loomis Laboratory, New York.

CASE XXVI.—Catarrhal pneumonia; cheesy foci in lungs; cardiac hypertrophy and dilatation; kidneys hard, congested, surface rough, cortex diminished. Adrenals: right normal; lower portion of left degenerated and converted into a white homogeneous substance. Microscopic examination shows the cells not filled with fat but with scanty protoplasm, leaving the nuclei intact in the centre of a reticulum. No necrotic areas; no congestion. Only a few normal cells are found, chiefly in the zona glomerulosa.

Semi-lunar Ganglia (of both sides). The nerve cells are distributed unequally throughout the ganglia. In many instances a definite sheath can be made out around them. Nerve bundles run through the ganglia at different points. Between the cells there is connective tissue with long oval nuclei resembling the nuclei of involuntary muscle. This tissue is most abundant where the cells are fewest. The nuclei are normal in shape. Nucleoli prominent. Many of the cells are pigmented with small golden-brown granules scattered through the protoplasm. They resemble hematoidin granules.

B. *Fatty Changes.*

CASE XXVII.—Cirrhosis of liver. Adrenals both contain considerable fat in cortices, the left more than the right.

CASE XXVIII.—Croupous pneumonia. Adrenals both very fatty.

CASE XXIX.—Lobar pneumonia. Adrenals both contain fat in cortices.

CASE XXX.—Cirrhosis of liver; pulmonary tuberculosis; chronic diffuse nephritis. Adrenals both contain much fat in cortices.

CASE XXXI.—Lobar pneumonia. Right supra-renal body normal. Left contains much fat.

CASE XXXII.—Ulcerative endocarditis; aortic insufficiency. Adrenals, both cortices fatty.

CASE XXXIII.—Lobar pneumonia. Adrenals, both cortices fatty.

CASE XXXIV.—Lobar pneumonia (bilateral). Adrenals both contain considerable fat.

CASE XXXV.—Aneurism of thoracic aorta; pneumonia; chronic diffuse nephritis. Adrenals both very fatty, the fat irregularly distributed throughout the cortex in patches of various sizes.

CASE XXXVI.—Chronic diffuse nephritis; entero-colitis. Adrenals both very fatty.

CASE XXXVII.—Myocarditis; diffuse parenchymatous nephritis. Adrenals both contain a great deal of fat diffused throughout their entire cortices.

CASE XXXVIII.—Aneurism of thoracic aorta; lobar pneumonia. Adrenals both very thick and contain much fat in cortices.

CASE XXXIX.—Pyopneumothorax; pulmonary tuberculosis. Adrenals both very fatty.

CASE XL.—Dilatation of aorta; cardiac hypertrophy: miliary tubercles in lungs; kidneys small, capsule adherent, markings indistinct. Adrenals. Microscopic examination: majority of cells in the zona fasciculata contain small fat globules of various sizes or one large globule displacing the nucleus. Some of these cells are distended. Other cells have lost their nuclei and are granular and necrotic. Portion of medulla next to cortex normal except for congestion, which is evident throughout the section.

The entire list of 112 cases, without symptoms of Addison's disease, includes: Extensive pigmentation; cloudy swelling from cases of infection from pathogenic organisms (*Brit. Med. Journ.*, May, 1889); atrophy, infiltration with small, round cells; fatty infiltration; tubercular inflammation (with bacilli); several simple cysts; two cases of hemorrhagic cyst; one of gumma; and a number of adenoma, sarcoma, and carcinoma.

Twice the supra-renal bodies have both been congenitally absent (Martini, *Comptes Rendus*, 1856, xliii. p. 1053; Spender, *British Medical Journal*, Sept. 11, 1858); and four times either the right or left has existed alone. Dr. Hartley recently told me that he has removed a supra-renal capsule in connection with excision of the kidney without the subsequent occurrence of any noteworthy symptoms.

In view of the opposing facts the immediate causative relation of supra-renal lesions to the symptoms of Addison's disease cannot be easily maintained in spite of their frequent coincidence, and we must seek a further explanation in the relation between the adrenals and the sympathetic nervous system. To this subject it will be convenient to return.

ADRENAL TUBERCULOSIS.

Two facts must be admitted regarding adrenal tuberculosis:

First. The supra-renal bodies are far more susceptible to tubercular inflammation than to any other form of disease.

Second. Addison's disease occurs oftener in conjunction with tuberculosis than with all other diseases together, or in approximately 80 per cent. of all cases. Hence, when tuberculosis invades the adrenals Addison's disease usually develops, although other and more important factors may be concerned in the process.

We find all the later stages of tubercular inflammation and of tubercular deposits in the adrenals, but their exact nature and extent have never been shown to bear any definite relation to the accompanying symptoms. Tubercle bacilli have been reported as present in the adrenals in a score of cases, but more often they are not found. In three recent instances the adrenals have given very marked reactions to inoculation with Koch's tuberculin, and in one of these there was extensive hemorrhage into the degenerated supra-renal body. In the great majority of cases both adrenals are involved; but when the tubercular process is present in but one, the left has been affected twice as often as the right.

The local tuberculosis frequently commences as a primary chronic inflammation, interstitial, and accompanied by the formation of small tubercles, which enlarge, coalesce, and degenerate to caseous masses that may soften and honeycomb the entire adrenal structure with cavities which are often described as containing pus, though the material is usually simple granular débris with oil globules. This substance may be replaced by calcareous matter, and sometimes, but less often, atrophy ensues. The inflammatory process commonly begins in the medulla and extends to the cortex, gradually obliterating all original structure, but the reverse may be the case, or both may be simultaneously affected. Adhesions and thickened masses of connective tissue, or deposits of fat are very apt to form about the adrenal bodies, and it is important to note that such changes often involve or include the adjacent sympathetic nerves and ganglia.

than tuberculosis deserves brief mention.

Malarial Fever. The accompanying anæmia of Addison's disease, and the fact that the spleen has certain physiological influences in regard to the chief pigment of the body, suggests the question, Whether malarial fever is associated in any special manner with the former affection? In the cases which I have personally seen there had been many attacks of malarial fever. Other observers have commented upon a similar coincidence. Lewin reports forty-five cases. But it has not been shown that Addison's disease is more frequent in those regions where malaria is most severe, nor does it bear any constant relation to malarial paroxysms when the two diseases coincide. The spleen is sometimes hyperæmic and is pigmented in Addison's disease, but it is frequently normal, and our present knowledge does not enable us to recognize an etiological relation between the two affections.

Carcinoma. With regard to carcinoma of the adrenals, whether it involves them primarily, as it has been rarely known to do, or by extension from contiguous organs, it is a remarkable fact that, as a rule, this lesion does not provoke either pigmentation of the skin, or typical symptoms of Addison's disease. Such a result has only once or twice been recorded (Fleiner, *Berl. klin. Woch.*, Dec. 23, 1889) The same may be said of sarcoma and adenoma.

Caries. Several cases of vertebral caries have occurred in conjunction with symptoms of Addison's disease, in which the local sympathetic system was also more or less involved.

Goitre. Three cases of coincident exophthalmic goitre have been observed. This fact is of special interest from the possibility of a connection having existed between abdominal and cervical sympathetic nerve lesion or irritation.

In general, it must be admitted that no other disease than tuberculosis accompanies Addison's disease with sufficient frequency to be regarded among predisposing causes.

Traumatism, or strain affecting especially the muscles of the back, has been reported several times as the exciting cause of Addison's disease in cases in which tuberculosis could be excluded.

In one instance the disease followed immediately upon a severe wrench of the back acquired while skating, and in another a fall into ice-cold water. Several cases have developed in connection with psoas and lumbar abscess from injuries of the spine.

AGE.

Addison's disease was originally held to belong only to adult life. Lately, however, two cases have occurred in infants only seven days old, and in one eight days old. All showed distinct bronzing. In one infant one adrenal was cystic and not caseous. Girode (*Bull. de Soc. Anat.*, April, 1891) reports the history of a newborn infant who had syphilitic adrenal gummata, without bronzing. Addison's disease has been observed in almost every year of life from birth to the eighty-first.

SEX.

Sixty per cent. of all cases occur in males.

DURATION.

While the average duration of all cases is from two or three months to a year, there are remarkable exceptions. One patient has lived ten years and another nearly eleven years (Schreiber, *Berliner klin. Woch.*, Oct. 13, 1890; Schmaltz, *Deutsche med. Woch.*, Sept. 4, 1890). A number of others are reported as living respectively four, five, seven, and eight years after pigmentation was first observed. It is difficult to account for the prolongation of life in a few cases of a disease which is so uniformly fatal at an early date.

SYMPTOMS.

Pigmentation. The belief that adrenal lesions are responsible in any direct manner for the bronzing of the skin and sometimes the mucous membranes is not sustained by analysis of reported autopsies. The theory has been advanced that the adrenals were more glandular structures than nerve organs (Virchow), and that the bronzing is due to a glandular chromogenic action of the supra-renal bodies. In other words, first, that they either alter normal hæmoglobin, constantly passing through their abundant bloodvessels and return it to the

blood; or, second, that they form new pigment when diseased: or, thirdly, that becoming diseased, a certain controlling influence ordinarily exerted over the blood pigment is removed. Many facts derived from a careful study of the embryology, physiology, and pathology of the adrenals are arrayed against these views.

The adrenals have long been known to furnish peculiar color reactions (Vulpian and Baunie, *Gaz. hebd. des Sci. Méd. Bordeaux*, 1888, No. 11). They become reddened by oxidation in light and air, are blackened by per-salts of iron, and turned green by dilute iodine solutions. Klebs has claimed that following irritation a chromogenic body is stored in the adrenal cortex in increased amount.

I have repeated the color-test with the adrenals of man and nearly all the domestic animals, and have never found them to fail. The deep green produced by brushing the freshly cut surface with sesquichloride of iron affects the medulla and not the cortex. This reaction is unique. Notwithstanding the peculiar color reactions, there is no conclusive evidence that the pigmentation of Addison's disease depends upon alterations in the blood, for the bronzing is often great while the blood is normal, and no excessive pigment has been found in it, neither is the urinary pigment increased. The only remaining hypothesis is that there is some peripheral sympathetic influence at work which causes the deeper cells of the rete Malpighii to appropriate and alter the blood pigment which circulates in the capillaries among them. This pigment is found in the protoplasm of the younger cells in the situation where it is normally present in the negro in excess, (Sjostrom, *Deutsch. med. Woch.*, May 30, 1889). Jürgens (*Deutsch. med. Zeit.*, May 10, 1888), believes that some pigmentary substances may be deposited through peripheral nerve excitation, originating in epithelial degeneration or external irritation, hence the pigmentation is most decided where the skin is exposed, in the face and hands, on flexures and folds, etc.

Gade (*Fortschritt. der Med.*, 1889, No. 12, p. 452), who has found pigmentary deposits in large branching cells in the velum palati and tongue, as well as in other mucous membranes and the skin, believes that the bronzing of Addison's disease is not the result of any specific action, but is merely an increase in the normal amount of pigment locally deposited from the hæmoglobin.

The fact has been confirmed by many observers (Lancereaux,

Nothnagel, Fleiner, *et al.*), that the pigmentation occurs most prominently in those cases in which the sympathetic nerves are found diseased. I have been told by Dr. C. S. Bull that he has examined the eyes of a number of patients with Addison's disease, but never found increase of pigment in the fundus oculi, though in one case it was present in excess in the iris.

I have above referred to 112 cases of adrenal lesion in which no bronzing appeared at any time. These abnormalities were of great variety, covering the range of pathological changes from simple hyperæmia to advanced caseation or calcification of the entire adrenal structure, yet at no period were the integument or mucous membranes pigmented in the slightest degree.

If the pigmentation of the surface depended upon functional derangement merely of the adrenals, by abolishing a control over the normal blood pigment, surely it could not be absent throughout widespread progressive destruction of their tissue. On the other hand, it cannot be alone due to new pigment formed by the supra-renal bodies, for fully 12 per cent. of all cases of typical Addison's disease have been unaccompanied by any adrenal lesion whatever.

Chemical analysis of the supra-renal bodies, in addition to the excess of pigment above described, shows that they contain leucin and myelin in quantities out of proportion to the number of nerves, also traces of hippuric, taurocholic, and benzoic acids, but nothing which is peculiar to the adrenals or which is not found in other situations in the body in greater amount.

OTHER SYMPTOMS AND VISCERAL LESIONS IN RELATION TO ETIOLOGY.

Careful analysis of the symptoms recorded in all cases of Addison's disease shows considerable uniformity in the occurrence of functional or other disorders of the alimentary canal and of the circulation, and suggests very forcibly the probable existence of a common cause to be found in disturbance of the abdominal sympathetic system.

Vomiting. In almost every case nausea and vomiting are present, and with asthenia they are often the first symptoms observed. The vomiting, at first paroxysmal, occurring at very irregular intervals, becomes more and more frequent and severe. It is not referable to

errors in diet, nor to gastric lesions. In a few instances slight gastritis or hyperæmia or pigmentation of the mucous membrane of the stomach have been noted, but these conditions are neither frequent nor prominent enough to account for the severe emesis.

It has been suggested that this symptom is due to an altered condition of the blood or to the presence of some toxine generated by the supra-renal bodies. But the vomiting may occur long before there has been time for alterations in the composition of the blood to appear, and the latter are usually neither frequent nor serious. It seems more probable that the emesis is due to an irritation of the cœliac plexus, which reaches the vomiting and respiratory centres through branches of the vagus nerve. We have many proofs of the possibility of this occurrence, and a functional irritation of the sympathetic nerves, even without destructive lesion, may be a sufficient factor, as in the vomiting of pregnancy, forms of severe abdominal pain like that accompanying the passage of gall-stones, or renal calculi, certain ovarian diseases, etc.

Diarrhœa. The same argument may be employed to account for the diarrhœa which is so commonly present. This is found to be more than twice as frequent as constipation, which as a rule occurs only at the commencement, and as in the case of vomiting, it does not bear any definite relation to errors in diet, nor is it excited by other common influences, such as exposure to changes in temperature, intestinal hyperæmia, etc. Lesions of the intestine, excepting occasional hyperæmia and ecchymosis and cases where general tuberculosis with ulceration exists, are so rare as to be regarded merely as coincidences. On the other hand, there is much experimental evidence in favor of the belief that diarrhœa, like emesis, is produced in this disease by splanchnic irritation rather than by altered blood or any other agency.

Lewin and Israel have shown that removal of the cœliac ganglion produces at first constipation and later diarrhœa, and the musculomotor and vasomotor impulses which emanate from it may be so modified by experimental irritation as to alter peristalsis, or produce local anæmia or hyperæmia. These results have been confirmed by others. In animals extirpation of the solar plexus gives rise to hyperæmia, ecchymoses and ulceration in the wall of the stomach and upper portion of the small intestine.

In a few instances atrophy or swelling and pigmentation of the solitary and Brünner's glands and Peyer's patches have been recorded, and this may be explained by the influence of the cœliac plexus through altered trophic impulses. That these lesions are not more frequent may be due to the fact that the trophic influence is not very strong or it is modified by the local plexuses in the intestinal wall.

Nothnagel has shown a relation to exist between atrophy of the intestinal wall and atrophy of the intestinal sympathetic plexus, although the splanchnic nerves were intact.

Changes in the other abdominal viscera are neither frequent nor extensive, and consist mainly of hyperæmia, which might also be due to sympathetic irritation or lesions.

The spleen has been found hypertrophic and often soft and pigmented, but it has been pointed out that the occurrence of coincident malarial fever with Addison's disease is not unusual.

The liver may be hyperæmic, cirrhotic, tubercular, or, as in one of my cases, syphilitic. There is nothing characteristic of Addison's disease in its various lesions. The mesenteric glands are frequently enlarged and caseous, but this is mainly in distinctly tubercular cases.

The kidneys and urine are usually normal, and mellituria has not been observed. Hyperæmia and moderate hypertrophy of the kidneys is reported in a few instances. This is also possibly due to blood stasis or altered blood pressure produced through splanchnic irritation.

Pain and tenderness. In fully one-third of the cases, sharp neuralgic or more often severe dull aching pains are present and referred principally to the lumbar region, but also to the deep epigastric and hypochondriac regions. The pain in several cases has been accompanied by extreme local soreness and tenderness on pressure (Henry, *Trans. Path. Soc. Phila.*, vols. v., x.). Müller (*Handb. der Physiol.*, i. p. 579) and Höffter (*Henle u. Pfeuffer's Zeit.* N. F. iv. S. 322) have demonstrated that experimental irritation of the cœliac ganglion gives evidence of acute sensibility, and severe colic may of course occur independently of serous or intestinal muscular lesions. It seems, therefore, probable that the lumbar and abdominal pains of Addison's disease may emanate from splanchnic irritation.

The lungs. In about two-thirds of the cases the lungs or bronchial glands have been affected in various ways. The majority of cases are tubercular. In other instances hyperæmia, œdema and pigmentation are recorded with pleuritic adhesions. Caseation and hypertrophy of the bronchial glands have been reported. The frequent occurrence of tubercular degeneration of the adrenals is thus explained in many instances as a secondary involvement, following the primary infection of intra-thoracic tissues.

Pulse. The modifications in the circulatory system are mainly referable to the pulse, which is uniformly small, compressible, and feeble, and usually rapid in the latter stages of the disease. Heart lesions are infrequent and the valves are usually normal. Atrophy of the heart has been observed twenty-seven times, and hypertrophy, brown pigmentation and fatty degeneration have occasionally been found. These conditions are too infrequent to account for the enfeeblement of the pulse, and since the latter may be present in acute cases when the blood appears normal and before the general nutrition of the patient is seriously impaired, it seems reasonable to believe that it is due to functional or reflex disturbances of the circulation coming from the abdominal sympathetic system.

When the vasomotor tone in the splanchnic system is lowered by experimental irritation, the general arterial pressure is reduced, producing cerebral anæmia and lessening the vagus tone. As a further result the pulse becomes quick, small, and compressible. The theory is advanced by Henry and others that a paralytic distention of the abdominal bloodvessels is produced, through functional or organic causes acting upon the sympathetic system, and thus disturbing the equilibrium of the circulation.

The central nervous system exhibits no typical lesions. Cerebral anæmia and hyperæmia are both recorded in about a dozen cases. Vertigo is frequently observed, and there is often mental weakness and depression with loss of energy. In protracted cases delirium and coma result, and in a few convulsions have been present. It is not uncommon for death to occur very suddenly through a condition resembling shock, or as it sometimes follows severe blows upon the abdomen. Patients are very apt to show more or less lethargy and mental dullness.

The asthenia, which is usually pronounced, appears so early that

there is no muscular atrophy and no loss of adipose tissue, and it is difficult to believe that it is not due to nervous influences rather than to changes in the blood, or malnutrition. Dyspnœa may accompany this condition.

The blood. Anæmia is common, but by no means extreme, and careful clinical study of the blood fails to establish satisfactorily the theory that the disease is essentially a blood disease. Free pigment is not found. While the red corpuscles may be diminished in number they do not appear otherwise abnormal, and in certain typical cases anæmia has not been present. In some of the more acute cases the symptoms become well-marked before the general nutrition has been appreciably impaired. The hypothesis that the symptoms are due to a toxine developed by the adrenals and discharged into the blood is not supported by evidence of value, and many facts are directly opposed to it. Ecker first described the adrenals as blood glands, in 1846, before Addison's disease was thought of, and recent inoculation experiments with the thyroid and various gland substances, and the general belief that the chemical composition of the blood is normally influenced by many different organs of the body, tempt one to regard the adrenals as possibly possessing a similar control, but the experiments upon animals, which I will presently report, fail to support this theory.

Rare symptoms have occasionally been observed complicating the usual type of Addison's disease, and they are of interest only in connection with the possibility of origin through extreme irritation of the sympathetic nerves. One instance of salivation is reported, one of bromidrosis and one of nutritive disturbance in the mammæ, uterus and other female generative organs. The mammæ and ovaries were greatly atrophied (Kleinwachter, *Lancet*, Jan. 25, 1891). The disease has once been observed in a "bleeder." (Schmaltz, *Deut. med. Woch.*, Sept. 4, 1890.)

The group of symptoms above considered, namely: the nausea; irritable paroxysmal vomiting and diarrhœa; localized lumbar and epigastric pain; enfeebled pulse; mental apathy and prostration; and the hyperæmia all point toward a common origin in a lesion which excites or irritates the abdominal sympathetic system, and not necessarily the semi-lunar ganglion alone, but at times the stomachic, hepatic, or mesenteric plexuses.

EXPERIMENTS UPON ANIMALS.

For the past four months I have been experimenting at the Loomis Laboratory upon the supra-renal capsules of various animals. Without entering too much into details in this paper, I will briefly state the results: The experiments were performed upon the cat, dog, rat, guinea-pig and rabbit, and consisted of transplantation, excision, and destruction of the adrenals, and inoculations of aqueous and glycerin extracts made from the adrenals of these animals, and from man in a case in which the capsules were obtained from an autopsy six hours after death from chronic cardiac disease.

Transplantation was performed by inserting the freshly excised adrenals from an animal of one species in the abdominal wall or abdominal cavity of another. After a few days or a week the adrenals were found degenerated, softened and apparently undergoing absorption.

Excision of the adrenals is one of the most difficult operations which I have ever undertaken upon animals, especially in the dog. They are so deeply situated that they are difficult to reach from behind, on account of the thickness of the muscles of the back, and if paproached from the front or side, so much displacement of overlying organs is necessary that irritation or injury of adjacent nerves is unavoidable. Moreover, in all the animals used a very large vein from the abdominal muscles lies directly across the ventral surface of the adrenals in a groove which divides them into two lobes connected by a narrow isthmus. This vein is joined by a relatively large branch from each supra-renal body. The latter usually lies on the right side in direct contact with the vena cava, and on the left with the renal vein. It is, therefore, almost impossible to ligate the muscle vein, and, of course hemorrhage from such a large branch of the vena cava or renal vein is soon fatal. To obviate this occurrence I have destroyed the adrenal bodies by the actual cautery. Animals thus treated make a good recovery and exhibit no symptoms. There is no increase in pigment of the mucous membranes or elsewhere, the blood is normal and digestion is good. A similar lack of symptoms is observed after transplantation of the glands.

A curious fact in relation to the adrenals has been observed by Stilling (*Virch. Arch.* Dec., 1889), namely, that in a young animal

after extirpation of one of these bodies the other hypertrophies to a considerable extent. The result would seem to indicate that the organ is not a mere relic of the embryonic state, but is of some unknown functional value.

Ablation of both adrenals is reported by many observers to cause death within a period varying from a few days to several weeks, and Tizzoni claims to have found resultant lesions of the nature of alterations in the walls of bloodvessels, hemorrhages, extravasations, and disturbances of the lymphatic circulation. He also claims to have observed in connection with the brain and cord, infiltration with leucocytes and fibrinous exudation, but these results have not been corroborated by any of the numerous experiments made by others when careful antisepsis is maintained.

Arnaud, Marino-Zuco and Guarnieri have extracted substances from fresh supra-renal bodies which they describe as acting as toxines. After using rigid antiseptic precautions they found that injection, even in small doses, of these materials subcutaneously or into the veins of dogs, rabbits, and guinea-pigs produces death in a short time.

One substance isolated by them is described as a phospho-glycerate of neurin. I have made a number of inoculation experiments upon animals with glycerin and aqueous extracts prepared from the freshly excised adrenals, and am convinced that if proper antiseptic precautions are employed the supra-renal bodies possess no toxicity when ingrafted or inoculated in animals.

An extract of both adrenals from a dog injected into another dog or into a cat or rabbit seems entirely without effect. In some cases I repeated the inoculations with the extracts several times in the same animal, which was kept alive for two months without symptoms.

Jaboulay (*Lyon Méd.*, Nov. 2, 1891), has described the occurrence of accessory supra-renal bodies situated upon the semi-lunar ganglion and in the midst of the solar plexus. I have several times observed these supernumerary bodies, and they have been reported as occasionally present in man.

Lesions of the sympathetic system.—It is greatly to be regretted that thorough microscopic examination of the abdominal sympathetic nerves and ganglia has not been more frequently made in the reported cases of Addison's disease, for there is good reason to believe that lesions can be very often found in these structures. The earlier

records are practically valueless in this regard, for they were made at a period when the technique of nerve preparation and staining was very imperfect as compared with present methods, and slight lesions even if sought for might have easily escaped observation.

The research of the past four or five years, however, is constantly bringing to light an increasing proportion of cases of Addison's disease in which the condition of the various sympathetic nerve structures is shown to be abnormal. The ganglia are often excessively pigmented, sometimes hemorrhagic. They may exhibit fatty degeneration, swelling, and even caseation and suppuration. Their nerve cells are atrophied, the vessel walls are thickened and infiltrated, the nerves have a thickened perineurium, and there may be degeneration of the axis cylinders. Such degenerative changes have been lately observed in the splanchnics, in the semi-lunar and solar ganglia, and in the plexus surrounding the abdominal aorta. Fleiner (*Berliner klin. Woch.*, No. 22, 1891), gives an account of two typical cases in which signs of inflammation were present in the ischiatic, crural, median, and vagus nerves. In one case there was a neuritis of the lower posterior spinal nerve roots, and some degeneration of the posterior columns of the cord. (Kalindero and v. Babes, quoted in Schmidt's *Jahrb.*, No. 1, 1893.) Such cases may be coincident with adrenal degeneration or occur without it; not infrequently the diseased adrenals are adherent to surrounding organs, and various sympathetic nerve branches are included in the proliferated connective tissue.

Armand and Alezais (*Semaine Méd.*, Oct. 7, 1891; *Marseilles Méd.*, Jan. 30, Feb. 28, March 30, 1892) have examined microscopically the lesions of a large number of cases, and they failed to discover nerve-cells in the medulla of the supra-renal bodies, but on their periphery, especially at the posterior surface are "pericapsular ganglia," which they declare are always implicated in Addison's disease, even when the semi-lunar ganglion and sympathetic nerves are not. On the other hand, Lewin (*Charité Annalen*, vol. x, p. 722) describes many axis cylinders in connection with ganglion cells in the adrenals.

I have been able to find only 81 published histories in which positive mention is made of the sympathetic system, and four of these may be regarded as incomplete, because no note is made of microscopic examination. Of the remaining 77 cases, 60 presented

decided lesions of the sympathetic nerves or ganglia. Among the 30 cases most recently examined 27 had such lesions. This is certainly a very striking fact taken in connection with the analysis of the symptoms of Addison's disease above given in which I have attempted to show the possibility of the direct cause being an irritation proceeding from the abdominal sympathetic system. Are we not in a position to adopt the following

CONCLUSIONS.

First. That Addison's disease is a condition arising from and dependent upon irritation of the abdominal sympathetic nerves through lesions of themselves, their ganglia, or diseased supra-renal capsules.

Second. In the great majority of instances (fully 80 per cent.) the disease originates as a secondary or primary tuberculosis of the adrenals, and the sympathetic system is either involved by extension of pathological processes, or is functionally disturbed and irritated through the intimate anatomical connection existing between the adrenals and the relatively large number of nerves which they contain.

Third. Actual lesion of the sympathetic system, while far more common than heretofore supposed, is not necessary to produce the varied symptomatic phenomena of the disease. Functional disorder, through irritation conveyed from the adrenals, may sometimes cause all the symptoms, just as in chorea and many of the conditions of aggravated hysteria, and other functional nervous disorders, we are often unable to find definite lesions.

Fourth. In a certain proportion of cases (not over 20 per cent.) the adrenals are affected by some other lesions than those of tuberculosis, or else they remain normal (in 12 per cent.) and the sympathetic nerves and ganglia are alone diseased.

I am aware that the objection may be raised that excessive pigmentation and even more extensive alterations are not infrequently found in the sympathetic ganglia, giving rise to no symptoms whatever (as in Case XXVI. above reported), and also that there is a tendency of late among physiologists to assign less independence and less functional importance to the sympathetic nerve system. In Addison's disease there are but three reasonable hypotheses to account for the

symptoms, namely, that it is a blood disease, that it is due to adnal toxines or that it is due to sympathetic irritation, either functional or organic. The latter hypothesis, while perhaps not wholly satisfactory, appears to be supported by much weightier evidence than either of the others.

While these views are not new (*vide* Greenhow, "On Addison's Disease," Croonian Lectures for 1875), by many they have not been finally adopted, for the reason that experimental and statistical data have been very slowly accumulated, and it has been my aim, by experiment and by analysis of all recorded cases, to place on a somewhat firmer basis the belief that Addison's disease is dependent upon lesion or irritation of the abdominal sympathetic nervous system.

DISCUSSION.

DR. PEABODY: It seems to me that discussion is likely to be lagging because Dr. Thompson has said it all. We owe him a debt of gratitude for his admirable deductions and conclusions from such a large number of cases of this rare disease, because it is only by a careful tabulation of this kind and equally careful deduction from it that any advance can be made in the knowledge of such a rare condition. I have had a number of cases of Addison's disease. I have one under treatment now who is improving, gaining weight steadily, about a pound a week for the last month, and is now going out of doors, although she had been bed-ridden for several weeks prior in consequence of an attack of grippe. I have also to add to Dr. Thompson's cases a case of tuberculosis of the adrenals in which there were absolutely no symptoms of Addison's disease except great weakness and death from asthenia. There was no pigmentation. The patient was a member of a physician's family and under constant observation. The condition was not suspected until after death, when I made the autopsy and found advanced tuberculosis of the adrenals and no other lesion.

DR. WELCH: I do not think it possible to draw any other conclusions than Dr. Thompson has drawn from his record of cases. I have seen six cases of Addison's disease, and all associated with the characteristic tuberculous lesion of the adrenals, and in two of these cases I found the tubercle bacilli, although I had to search for them a long time. I was rather struck in these cases with the unusual localization of the tuberculous lesion. In one case there was tubercular deposit in the bodies of nearly all of the vertebræ. There was no deformity of the vertebral column, for there was not sufficient destruction

of bone to bring that about. In another case there were tuberculous lesions in the mesenteric glands and in the genital tract, but nowhere else in the the body. In looking over the record of cases at that time I was impressed with the fact that tuberculous lesions associated with Addison's disease are often peculiar in localization. A few months ago a negro came to autopsy at the Johns Hopkins Hospital. He had been in the hospital only a short time, and at the autopsy we found characteristic tuberculous disease of both adrenals. There had been no suspicion of the existence of Addison's disease. Having our suspicions aroused by this condition of the adrenals, we examined carefully the mucous membranes and found abundant dark pigmentation of the mucous membrane of the gums and on the sides and back of the tongue. This raises the question as to how a diagnosis is to be made of Addison's disease in the negro. The mucous membrane of the gums and of the tongue in the negro is very often pigmented in life, much more frequently than in white people.

DR. WHITTAKER: I have seen two cases of Addison's disease in the last five years, and both of them showed caseous masses in the adrenals and one evidence of tuberculosis elsewhere. The diagnosis was established by the digestive and nervous symptoms and discoloration of the skin. This discoloration of the skin occurs, not as an abnormal deposit, but as a physiological plus. It is an over-accumulation of pigment in places where pigment usually occurs. We most readily arrive at a diagnosis by uncovering the body and observing the linea alba, nipples, scrotum, and axillary region. It is something of a surprise to me to learn that in so large a proportion of cases the pigmentation was not due to disease of the adrenals. So far as my reading and study of the subject goes, in the great majority of cases disease of the adrenals was found. It may be that the failure to obtain the discoloration in the experiments of the essayist may be explained by the fact that the animals were not kept long enough. Tizzoni found that when rabbits were kept for two and a quarter years after crushing the adrenals the pigmentation always occurred. Brown-Séquard's theory has been recently revived by Tschirkoff, to the effect that it is the function of the supra-renal capsules to remove the pigment from the body, and that the disease of these supra-renal glands destroys this power, and hence the pigment accumulates. These cases have been hitherto hopeless. It was a great comfort to believe that the disease is caused by tuberculosis, for if it be a pure tuberculosis it may be amenable to some relief.

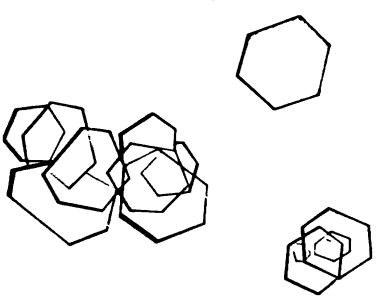
DR. THOMPSON: I have nothing to add, but I desire to emphasize once more the interest that attaches to careful examination of the abdominal sympathetic nerves and ganglia where cases of Addison's disease are recognized, and to urge that those who have opportunities to make pathological examinations do not overlook this point.

TWO CASES OF CYSTIN CALCULUS.

By JAMES TYSON, M.D.,
OF PHILADELPHIA.

CASE I.—M. C. H., a native of Pennsylvania, a salesman, consulted me in September, 1888, being at that time twenty-three years old. He had always enjoyed excellent health until two months before his visit to me, when he had a severe attack of malarial fever, during which he lost twenty pounds, which he has, however, since regained. Four weeks later, while still suffering from malaria, he was seized with severe pain in the left flank, which lasted only five or six hours, being replaced by a more moderate pain, which continued up to within a few days of his visit to me. The *urine* brought to me had a specific gravity of 1025, and contained a copious flocculent sediment composed entirely of beautiful six-sided tablets of cystin like those of the drawing, which was made from a slide.

FIG. 1.



Cystin crystals from urine.

He was ordered fifteen grains citrate of potassium in eight ounces of water three times a day. The discomfort referred to continued, more or less, until October 21st, when he again had a severe paroxysm, which was promptly relieved by fifteen-grain doses of antipyrine.

Examinations of the urine, November 15, 1888, December 5, 1888, January 1, 1889, March 1, 1889, all recognized copious sediments of cystin. After the last date I did not hear from him again until October 15, 1892, when he called upon me, having in the meantime removed to Michigan. He had been without

pain during the two and a half years interval until August, 1892, when there was a recurrence in the left flank, followed by another attack a week later. Since then, up to the time of his visit, he had been tolerably comfortable, although working hard night and day for three years past. Specimens of urine brought to me at the time, representing the urine of rising and retiring, contained large sediments of cystin. I then directed him to take half a drachm of aromatic spirit of ammonia four times a day, the treatment being based, as was that first directed, on the well-known fact of the solubility of cystin in alkalies.

On October 18th he had a slight attack of pain. On November 11th he sent me a small oval stone 6.25 mm. by 3 mm., which he had passed without pain, and which on analysis I found to be pure cystin. On December 6th he passed without pain a couple of small stones, which were not sent to me. On December 11th he had a sharp attack lasting twenty-four or thirty-six hours. On December 30th I received samples of morning and evening urine, both of which contained cystin, though in smaller quantity than previous samples. During this time he was taking aromatic spirit of ammonia. He wrote also that he had been free from pain since his last paroxysm.

On January 6, 1893, I wrote him directing the substitution of citrate of potassium for the aromatic spirit of ammonia. On February 5th, while still taking the potassium citrate, he wrote to say he had some pain in the left flank immediately after the change of treatment, but since then had been entirely free. He also sent samples of morning and evening urine, both of which contained an abundance of cystin crystals, the evening specimen much more than the morning.

About March 1st he had a sharp attack of nephritic colic, requiring the hypodermic use of morphine, and on March 5th passed the largest stone shown. —6.25 mm. in diameter. At the beginning of this attack the physician in attendance substituted the aromatic spirit of ammonia for the citrate of potassium. This was continued, and on March 13th, morning and evening samples were again sent, in both of which the cystin was present, but in much smaller quantity, especially the morning secretion, in which I found only two crystals in a single field of view with a one-fifth objective, and although they were more numerous in the evening urine they were still few as compared with other samples. With a view to information on the well-known fact that cystin sediments are sometimes hereditary, I asked for a sample of urine from a member of his family, and he sent me that of his brother, a vigorous young man of twenty-six years. There was no cystin whatever in it. The citrate of potassium was continued.

On April 19th, the patient sent me some minute spherical calculi, perfectly smooth as contrasted with the others, of which some are shown, and of which he said himself they looked as though they had been reduced in size by the action of some solvent substance.

Samples of the morning and evening urine were last received May 27th, the patient having been taking the citrate of potassium regularly and at the time

of sending. He wrote me that when tested by litmus paper the urine was nearly always alkaline, but both samples received by me were acid and contained a small flocculent sediment composed of cystin.

He wrote also that he had had no trouble for a month, except a little pain in left flank two weeks prior to the writing, when he had a little pain in the left flank, and had passed "quite a lot of small gravel from May 1st to May 10th, but since the 10th none at all."

From such therapeutic observation as I was able to make in this case, it would seem that the continuous use of the citrate of potassium in doses sufficient to alkalize the urine tend to keep cystin in solution, and also, possibly, to dissolve the concretions themselves.

CASE II. was that of a practising physician, G. B. W., aged forty-five, a native of Lancaster Co., Pennsylvania, and residing there when he came under

FIG. 2.

Calculus with nucleus of pure cystin and exterior of mixed phosphates. Nat. size. 1, nucleus.

my observation, January, 1879. Thirty-seven years before I saw him, that is, when eight years of age, he was lithotomized by Dr. Nathan R. Smith, of Baltimore, Md., and a calculus said to be pure cystin removed. Half of this calculus is now in my possession. It is oval, and measures 4.5 cm. by 3 cm. Instead of being composed of pure cystin, however, only the nucleus, measuring 1.5 cm. by 1 cm., is cystin. (See Fig. 2.) The cystin has the usual yellowish, beeswax-like appearance and softish consistence, being easily broken by the finger-nail. It does not exhibit the emerald-green tint said to be assumed when the cut surface is exposed to the air. The remainder and larger portions of the calculus, composed of the "mixed" or fusible calculus and phosphate of lime, are concentrically arranged. He continued to pass cystin daily through life, although a specimen examined before I visited him at his home contained only pus and a proportionate amount of albumin. For some time previous to this he had suffered with numerous severe attacks of nephritic colic, among the con-

sequences of which was obstinate nausea, making it almost impossible to retain anything on his stomach. This, with the exhausting effect of the pain, wore him out. At my visit I was satisfied that a calculus was somewhere impacted in the urinary tract.

He died on March 6, 1879, and Dr. William B. Rowland, of Rowlandsville, Maryland, wrote me an account of the autopsy. A calculus was found in the left ureter, just ready to pass into the bladder. Behind the calculus, and outside the ureter, was a collection of pus, dipping down into the pelvis, which Dr. Rowland said would have made its exit through the ischiatic foramen had he lived. It was as large as a pea, and roughly granular. A single large biliary calculus was found in the gall-bladder, occupying its entire extent. The composition of the urinary calculus was not determined. One of the kidneys was much reduced in size, but both were reportd as otherwise normal.

Since the announcement had been made of the intended report of these cases, I have received a letter from Dr. James E. Reeves, a member of this Association, stating that in forty-three years' experience he had seen but one case of cystin calculus, fifteen years ago. The patient was a woman, nearly sixty years old, who had suffered more or less from "kidney and bladder trouble." One day, while sitting on the seat of a garden privy, she was seized with great pain about the orifice of the urethra, and her cries were so loud as to alarm the family. She was carried into the house, and Dr. Reeves sent for. After some difficulty the calculus was extracted, and proved to be cystin. It was cartridge-shaped, an inch and a quarter long, and five-eighths of an inch in diameter.

DISCUSSION.

DR. WHITTAKER: I would like to ask the Doctor what is the origin of cystin.

DR. TYSON: I do not know, nor do I know that anyone else does.

DR. WHITTAKER: I asked only to get Dr. Tyson's valuable opinion concerning some very fine observations by Brieger in regard to cystin. He derives it, as a ptomaine, from the alimentary canal. He finds it always in combination with diamine, and assumes it to be found only in connection with infectious diseases. In these cases of Dr. Tyson the occurrence of cystin in the urine is a life-long condition, and that is, of course, incompatible with the view that it occurs only in the course of any ordinary infectious disease.

ON A SIMPLE CONTINUED FEVER.

By G. BAUMGARTEN, M.D.,
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DURING the last fifteen years, and longer, in St. Louis and its vicinity, there have come under observation numerous cases of a continued fever, which often are classed with typhoid fever, and by some —with little regard for accuracy of meaning—called typho-malarial, though differing widely from Woodward's "typho-malarial." Let me name it, provisionally, a simple continued fever, so long as we have no positive knowledge of its etiology—basing the term "simple" upon the absence of all signs of localization, and eschewing the names typhoid and typho-malarial, because the cases in question lack the chief characteristics both of typhoid and of malaria.

Having seen, in the course of years, a goodly number of such cases —say one hundred and twenty-five—many of which were entirely uninfluenced by medicinal treatment, I am prepared to give an account of the natural history of this form of fever.

In brief words, it is a fever running, if left alone, a favorable course of from four to five weeks—with rather more tendency to true relapses than typhoid fever—with relatively high temperatures, even hyperpyrexia, but without any essential disturbances of the digestive, respiratory, or nervous system. It has a decided predilection for youthful individuals (my cases ranging from the second to the thirtieth year).

A clear conception of the disease is, perhaps, most readily formed by comparing it with the typical picture of a moderately severe typhoid fever. But before drawing this parallel, I must protest against the assumption that I am describing either *abortive forms* or *mild grades* of typhoid; the very high temperatures, together with the long duration, should alone suffice to guard againt such diagnosis.

Considering, first, the course of the fever, we at once meet with considerable differences. Although it is true that one group of these cases begins with a steadily rising fever which, step by step, gains its height about the sixth to tenth day, and develops a temperature-curve very similar to that of typhoid; yet there is another group, about equal in numbers, in which the onset is quite sudden; the physician discovers the patient in high fever, yet suffering surprisingly little. In either group, the progress of the fever is subject not only to considerable variations in one day, but to great irregularity of the daily means. Sometimes, a few days of weakness and malaise, less often of headache and muscular pains, precede the fever; in other instances the fever is initiated by a chill. About the end of the fourth or fifth week the temperature in some cases suddenly drops to or below the normal, with no other critical phenomena than perhaps a profuse sweat. Such termination by crisis, though frequent, is not the rule, however; more often the fever sinks, as in typhoid, by lysis, but occasionally flares up once more to a high temperature before it subsides altogether. The highest temperature I have observed was 106.4° F. in the axilla.

As in the epidemics of true typhoid, here also we meet with a number of cases of short duration, terminating after fourteen to eighteen days. Not all of these aborted cases are mild, however, as judged by the temperature (and it is the temperature alone which can serve in this disease as a criterion of mildness or severity, since all other symptoms, as will be seen, are only *pari passu* concomitants of the fever).

As to the daily variations, not only individual cases but different stages of the same case behave very differently; morning remissions are the rule, with exceptions, but *regular* evening exacerbations are rare; frequently, the temperature is highest soon after noon; sometimes the maximum falls about midnight. But even this behavior is not constant in the same case. At times the daily oscillations are very small (1° F.).

There is no other disease within my knowledge in which the temperature of the skin is so deceptive; in which it is so little possible to judge of the height of the fever by the warmth of the skin as felt by the hand. It is frequently observed that with an axillary temperature of 104° the skin of the extremities, even of the trunk, gives

the impression of apyrexia. So burning a skin, as in scarlet fever, or even in typhoid, is never felt. A series of measurements of the cutaneous temperature, which I made in 1889–90 in cases of this and other febrile diseases, confirmed the impression which the sense of touch gives: the skin really is relatively cool; and they showed, moreover, this noteworthy behavior: while in scarlet and some other fevers the heat of the skin rose and fell somewhat parallel with that of the blood, in *this* continued fever (and also less markedly in typhoid fever) its rise commonly coincided with a fall of the internal temperature, and *vice versa*. (See temperature charts V., VI., and VII., p. 74.)

The pulse-rate does not usually keep pace with the temperature, but is apt to lag behind, and drops sooner than the temperature. *E. g.*, on one day, with a temperature of 103°, the pulse was 108; on the next day, with the same temperature, pulse 92; on the third day, temperature 100°, pulse 88. This behavior was constant enough to enable the physician to predict, from a fall of the pulse-rate, an abatement of the fever on the following day. Even in the later stages the pulse does not reach the frequency of the pulse in typhoid of equal temperature, except in very debilitated patients. Yet the pulse-tracing usually shows the degree of dicrotism which corresponds to the temperature.

The disturbances of the nerve-centres, compared with those which the typhoid patient with equally high fever presents in the same stage of the disease, are extremely slight. Only a minority of cases show distinct muscular and articular pains. In two instances, it is true, I have witnessed pain in the back and limbs in an eminent degree, lasting several days. Headache and sleeplessness are seldom observed, confined to the beginning of the illness, and of short duration; and although many of these patients sleep a good deal, sopor and hebetude of mind are absolutely wanting. Delirium is more frequent, but confined to the night or to periods of highest fever, and some cases with extremely high temperatures remain free from delirium throughout. On the contrary, the youthful patient is often enough found in high spirits, inclined to talk, read, play checkers, perfectly clear in mind, and quite unconscious of his high fever; while the thermometer in the axilla registers 104° and more day after day, he pleads to be allowed to get up next day, to go to school next week —a thing unheard of in typhoid of corresponding severity. Mut-

tering delirium, subsultus tendinum, involuntary urination, etc., are unknown.

These observations, which repeat themselves again and again, conflict with the current assumption that the nervous symptoms in question are due, or mainly due, to the high temperature. Among later authors, Jürgensen, *e. g.*, says, in connection with typhoid fever: "There is no well-founded doubt but that the signs of disturbed cerebral function are, with rare exceptions, consequences of the rise of temperature." (*Lehrbuch d. spec. Pathologie u. Ther.*, 1886, p. 277.) But this view seems to be contradicted point-blank by the common experience in this disease. With degrees of heat quite as high as ever in typhoid, the cerebral symptoms are incomparably less severe, and by no means characteristic. My own interpretation would be that while in typhoid the toxic agent affects the nerve centres severely, in the disease under discussion it affects them (excepting the thermic centres) but slightly.

With equal distinctness this continued fever differs from typhoid by the complete absence of intestinal lesions. The entire digestive apparatus commonly suffers no more than in any other febrile disease, or less. There is some loss of appetite, sometimes complete for a few days, and perhaps a coated tongue; but the tongue usually loses its fur long before the fever abates, and in many cases a very fair appe tite returns. As a rule, in spite of the fever, it is easy to nourish these patients fairly well. The dry, red, glazed, typhoid tongue, the black sordes on teeth and lips, are always missed. I have never encountered angina or parotitis. Diarrhœa is rare, and never continuous, nor severe, nor characteristic; no pea-soup stools; in those cases in which diarrhœa set in at any time, the stools were either dark-brown and fetid, or greenish and mucous. Constipation is more frequent. But a normal stool is almost the rule. Meteorism is not frequent, nor of high degree—more frequent in connection with constipation than diarrhœa. Nor have I ever been able to elicit marked tenderness on pressure, or gurgling, in the ileo-cæcal region. It appears unlikely, therefore, that ulceration or catarrh of the small intestines have any part in the disease. Post-mortem evidence is wanting, for there were no fatal cases.

Moreover, enlargement of the spleen is wanting. In only one case was the spleen found enlarged, in an adult—an instance which, in a

malarial country like ours, it seems fair to deem an accidental coincidence. I may lay stress on this point, because search for splenic enlargement has been thorough in every case.

Excepting a slight bronchial catarrh in two instances, the respiratory apparatus was not involved. Sometimes, during the acme of the fever, a hacking, irritative cough appears, which ceases at once on the remission of the fever.

In six cases (of forty-eight examined) the urine contained traces of albumin,[1] but no casts; nor was there ever any other evidence of renal lesion. In the first week the urine is apt to be scant, heavy, dark yellowish-red, loaded with urates; later it is apt to be scant, but of normal color and specific gravity, even while the temperature is high. In the fall of 1889 and in 1890 I applied the diazo-reaction test to every case, without a single positive result. During the late epidemic of typhoid fever in our city (October to December, 1892), I applied the test to every case of simple continued fever in which diarrhœa occurred at any time, and while the diarrhœa lasted, likewise with a uniformly negative result.[2]

The skin shows neither rose spots, nor herpes, nor petechiæ; one case presented an erythematous blush on the chest, lasting a few hours; another was complicated with urticaria. The course of the disease is not aggravated by bedsores, nor is it followed by loss of hair to any like extent as typhoid fever. During the later weeks the skin is often moist; copious perspiration has been seen only in those cases which at any time experienced, or ended with, a sudden fall of temperature.

The emaciation is usually great, though not so great as is common in typhoid—as follows naturally from the absence of diarrhœa and the better condition of the digestive system. During convalescence, the patients acquire the same active appetite and rapid gain in body-

[1] In one case, only once in the first week: in the other cases during three to five days, never after the fourteenth day of the disease; in one case during five days of the relapse.

[2] During the prevalence of this epidemic (in which the number of typhoid cases did not equal the number of cases of this continued fever), there occurred numerous cases of diarrhœa, lasting from one to ten or twelve days, intractable to ordinary remedies, but improving under salol, salicin, phenacetin, and the like, which were commonly interpreted as influenza. These cases almost invariably gave a positive reaction with Ehrlich's test. My friend, Prof. C. O. Curtman, who called my attention to the fact, had the same experience.

weight and, later, the same blooming health as in a thoroughly healed enteric fever. In two cases subacute, moderately painful, articular inflammations occurred; these arthropathies affected chiefly the wrists and ankles, were not accompanied by fever, and of only a few days' duration. Apart from these instances, I have observed neither complications nor sequelæ.

Without complete statistical notes, I have gained the impression that true relapses were rather more frequent in this than in typhoid fever. Most of these relapses—which began on the fourth to seventh day of apyrexia—ran a course of equal severity and almost equal duration as the primary attack, and with very high temperatures; surely, if this were typhoid, such relapses were calculated to bring out the marks of the typhoid process.

I will add that in several cases diligent search has been made for the malaria plasmodium in the blood, without success.

From what has been said, it follows that the differential diagnosis between this fever on the one hand, and malaria or typhoid fever on the other, cannot be difficult—except that the first week or ten days, perhaps, may not decide against typhoid. Nevertheless, in my contact with professional colleagues I learn that many, in spite of often-repeated experience, invariably consider or suspect such cases at the onset to be malarial, and fill the patient with quinine; and when the case does not yield to quinine, and the fever continues—as it will—they call it typho-malarial, forsooth!

As against typhoid fever, the temperature-curve is not typical, and the gradual stepladder ascent is often wanting; more frequently the fever is high from the first; there are wanting the epistaxis, the bronchial catarrh, the rose spots, the splenic tumor, the ileo-cæcal tenderness, the diarrhœa; and the sensorium remains clear. In the sequence, also, the so-called typhoid symptoms do not develop; there is no sopor, no deafness, no coma vigil, no subsultus tendinum; nor do we see the dry tongue with its glazed cup. No hemorrhage from the bowel, no fatal perforation; and, indeed, within my experience, no fatal case. The fact that some cases which in the end prove themselves typhoid by a perforation or a hemorrhage, have in the earlier stages been confounded with this fever, cannot militate against the view that the two are distinct pathological processes. In short, I regard the absence of all signs of localization as the key to the diagnosis.

The points of *resemblance* with typhoid fever, are, then: (1) The continued fever; (2) the lassitude and prostration, and in most cases the loss of appetite, enfeebled digestion and consequent emaciation; (3) the limitation to a period of from three and a half to five weeks; (4) the liability to relapse.

The points of *difference* are, briefly: (1) Differences in the temperature-curve, especially the frequent hyperpyrexia at the onset, or at least a sudden beginning, and the occasional termination by crisis; (2) the absence of all signs of localization, notably of intestinal affection, enlargement of the spleen, or rose spots; (3) the absence of the so-called typhoid symptoms, notwithstanding prolonged high temperatures—even in the relapses.

Now, bearing in mind these important differences, the points of resemblance can justify a diagnosis of typhoid fever in such cases *only on this condition*, that we are prepared to call every continued fever not otherwise explained, a typhoid fever.

From the remittent fevers of malaria our fever is marked off by the absence of intermissions in the pyrexia, the more decided remissions even being rare and irregular—by the absence of icteric complexion, of gastric disturbance, of congestion of liver and spleen. These differences are accentuated by the utter inefficiency of quinine.

Far from considering this disease, therefore, as a combination or hybrid of malaria and typhoid, I feel justified in denying both elements. All the actual symptoms of the disease can be explained directly as symptoms of fever *per se*.

I am fully aware that there is something still wanting to the full history of these cases which might bring out decisive points of identity or difference, namely: (1) The post-mortem demonstration of the presence or absence of the characteristic enteric lesions; but the opportunity for this is rare and must be accidental, since no case within my knowledge has proved fatal. (2) The demonstration of a common etiology in this fever and the usual typhoid. This line of investigation has yielded no positive information as yet, and the scattered cases of a private practice in a large city promise only uncertain results in this respect. (3) A thorough bacteriological investigation might prove or disprove identity of the morbific cause. This research has not yet been made.

The treatment requires but few words. The high temperatures

have indeed—too frequently, I fear—led me to use antipyretic drugs, quinia, antipyrin, and, later, phenacetin. The two latter, at least, are sometimes justified in that they procure a sense of relief and comfort by removing temporarily the entire group of symptoms of which this disease can boast—the fever symptoms—except the debility; a sense of comfort much greater, on the whole, than the same means afforded in typhoid. None of these remedies abbreviates the disease. Cold ablutions and cool baths have been resorted to with similar effect. Of late, I have usually refrained from all antipyretic means, unless the patient not only had a high temperature, but showed that he suffered from it. Beyond this, the treatment was purely dietetic and symptomatic. A large number of cases were treated without drugs save alcohol. I would strongly urge a treatment which interferes as little as possible. If others have observed, along with the high fever and the symptoms obviously resulting from it, an unusual severity of the course or troublesome complications, this surely may be ascribed in part to meddlesome medication; in more than one case, in which the active antipyretic treatment by quinia, salol, antifebrin, antipyrin, etc., was discontinued at my suggestion, all threatening symptoms abated in spite of the continuance of undiminished fever.

The sketch which has been presented to you was, in the main, embodied in a paper which I had the honor to read before a small circle of medical friends four years ago, and is based on observations which began about 1876. If such cases occurred in the earlier years of my practice I have overlooked them. In 1880, the disease was discussed in the medical societies of St. Louis, and a committee of the Board of Health of that city canvassed opinions on its nature and origin. It is not surprising that the answers elicited by this committee related to all sorts of cases, according as the questions were understood, not only of this but of typhoid and other fevers as well, nor that the resulting report interprets the disease as a "mild expression of the specific poison [of typhoid fever.]" The word *mild* rather avoids the main question.

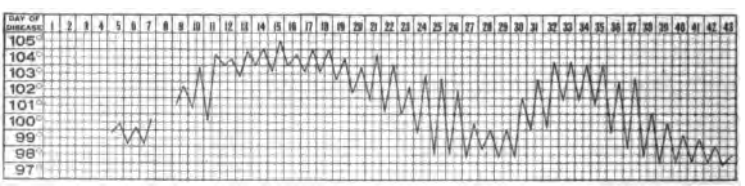
At the meeting of this Association in 1887, Dr. Atkinson, of Baltimore, spoke of "Forms of typhoid fever simulating remittent malarial fever," and related cases which answer in many particulars to those of which I speak to-day. Yet they also differ enough to leave some doubt whether we refer to the same thing. In he following

year, my colleague, Dr. P. Gervais Robinson, of St. Louis, submitted a short paper on cases of continued fever that are certainly of the same nature as those which I have attempted to sketch. During the months of October, November, and December, 1892, St. Louis was visited by an epidemic of typhoid fever. Both before and during this period there was also an increase in the frequency of the continued fever under discussion. The latter became an object of frequent observation and comment by many observers, and so generally recognized were the incisive points of difference between the two, that some, who could not break away from the idea that all cases of continued fever occurring at this time must be of the same nature, expressed a doubt whether there was any typhoid prevailing at all—a conclusion which abundant post-mortem evidence of typhoid, of course, proved incorrect.

The briefest manner of giving the history of these cases, in the absence of symptoms not directly referable to the fever, seems to be to present records of the temperature, with comments. Cases I. and II. are examples of more or less gradual beginning; the temperature-curve of Case I. looks, indeed, like that of a typhoid with the initial stage long drawn out.

CASE I.—Boy of ten. (First ten or twelve days under the care of my friend, Dr. W. E. Fischel.) A slight hacking cough during the height of the fever, from the fifteenth to the eighteenth day. Much perspiration twenty-fourth to twenty-sixth. Relapse on the thirtieth. Nightly delirium on the thirty-

CASE I.

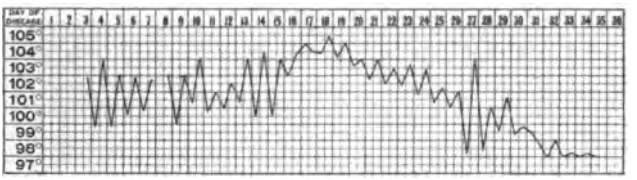


second to thirty-fifth. A bilious diarrhœa for two days of the acme of the relapse, easily controlled by salicylate of bismuth. No treatment except cold sponging, wine, and infrequent doses of phenacetin. Took nourishment fairly well.

CASE II.—Young lady of about twenty-four. Rise of temperature rather more rapid, without subjective symptoms except weakness. Spent her days in a chair or on a lounge until the seventeenth day, when in the early morning a chill and vomiting set in, lasting an hour, with an axillary temperature

of 105°. After this, she spent a few days in bed. No other symptoms. Nutrition unsatisfactory, but loss of weight not excessive. Convalescence rapid from the thirty-second day. No loss of hair.

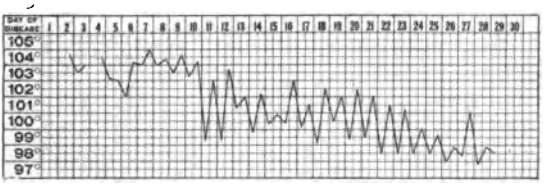
CASE II.



Cases III. and IV. are of the class which set in suddenly.

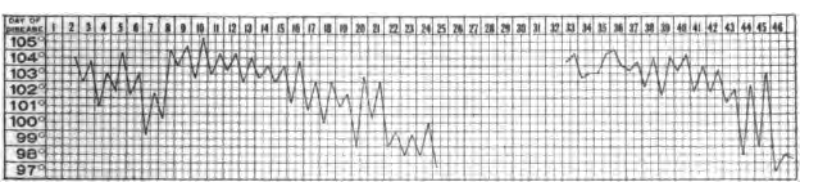
CASE III.—Young lady of about twenty-two. Suffers from nervous excitation, insomnia, slight nightly delirium and total loss of appetite from the seventh to tenth day. During the week following the appetite was capricious. Duration twenty-eight days.

CASE III.



CASE IV.—Schoolboy of fourteen. Began suddenly with a chill and severe headache during the morning hours at school. Since then, no symptoms but weakness and fever. Appetite good or fair throughout. At noon of the thirteenth day he sits up in bed playing checkers, and asks to be sent back to school

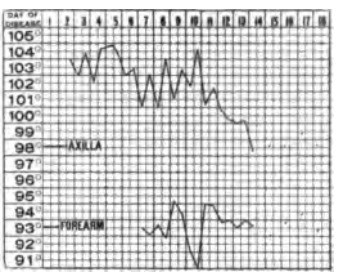
CASE IV.



next week, temperature 104°. Relapse on thirty-second day. On the fortieth day is found at noon sitting up in bed eating a hearty meal, and asks to be permitted to get up and dress, temperature 103¾°. Never any delirium; abundant sleep; no diarrhœa; slight constipation at the end of the relapse.

Cases V. and VI. are examples of short duration, one with gradual, the other with sudden beginning. No symptoms beyond the fever. Observations on cutaneous temperature were made in these cases.

CASE V.



CASE VI.

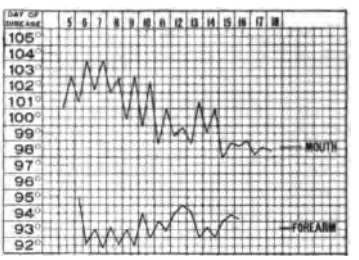
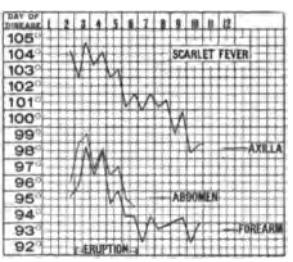


Chart VII. is added to illustrate the behavior of the cutaneous temperature in a case of scarlet fever. (See page 66.)

CHART VII.



All the cases here given not only recovered, but have been in perfect health since; and recovery was not followed by loss of hair. A number of cases of mild typhoid fever observed during the same years, with lower averages of temperature and of shorter duration, were accompanied by rose spots, ileo-cæcal tenderness, characteristic diarrhœa, mostly with enlarged spleen, and followed by more or less complete loss of hair.

DISCUSSION.

DR. ATKINSON: Typhoid fever is the great, the almost universal, continued fever, and in our experience we find that most of the new continued fevers that from time to time have been written about are sooner or later relegated to the class of typhoid fever. Thus we find that typho-malarial fever has been definitely determined to be typhoid. When we go into countries where malarial fevers do not prevail we hear of mountain fevers, mucous fevers, gastric fevers, nervous fevers, etc., but sooner or later they have all become classed as typhoid fever. Dr. Baumgarten has referred to a paper which I read three or four years ago, and thinks that he recognizes in the cases which I reported cases that are of the same character as his own, and I feel, therefore, a little more confidence in believing that the cases he describes still belong to the class of typhoid fever and are varieties of typhoid fever. We should recognize the fact that typhoid is a most capricious disease, that it is atypical in very many cases. The typhoid fever of the class of people to whom he especially refers, of children, is especially atypical. It is a common thing for all the characteristic symptoms of typhoid, except fever, to be absent in children. If I recognize the class of cases which Dr. Baumgarten has described, I think I am constantly meeting them. They run the course which Dr. Baumgarten has described, and one can pretty confidently predict the course which such a fever will run. Dr. Baumgarten has referred to the fact that where the fever runs its course, and then develops the symptoms of typhoid, it is not fair that his position should be weakened by that fact. Suppose, on the other hand, that such a fever did not develop typhoid symptoms, then he claims it as one of his class. We are all familiar with cases running the course that Dr. Baumgarten has described, and then developing unmistakable symptoms of typhoid. We see cases of most undoubted typhoid fever without the development of high fever at all, and then again we see it running two or three weeks, and then lighting up, and having even hyperpyrexia. These cases, running such different courses, are due to the same origin. In one case, a young man having high fever, but an unclouded mind, and playful and cheerful, with a desire to be up, to eat, and having all the symptoms corresponding to those described in the paper, has, at a distance, a brother who had lived in the same house with him, and been exposed to the same influence, who has concurrently the typical symptoms of typhoid fever. It is true that these cases usually run a favorable course, but it is also true that occasionally we meet with cases in which the disease, after running this course for one to three weeks, will develop undoubted symptoms of typhoid. I think we need a good deal more evidence to make us accept the existence of another independent continued fever.

DR. BAUMGARTEN: Dr. Atkinson still insists on the classification of all cases, no matter how "abortive," under the name of typhoid. But let us look at analogies with other diseases. We have a bronchitis that is

tubercular, and much more bronchitis that is not tubercular; we have an angina that is diphtheritic, and anginas that are distinctly not diphtheritic; and as regards the argument of a case in the end proving to be typhoid after all, we have just such cases of supposed follicular angina which, after they have run a certain number of days, suddenly develop diphtheritic symptoms, and turn out to be diphtheria. I am very far from meaning to prove anything by this analogy, except that it is at least reasonable to suppose that there are continued fevers which are developed by the specific typhoid germ, and others, running perhaps a similar course as far as the fever is concerned, that are not so caused. Unless we look at the cases with the bias of "if they are not typhoid, what are they?" we have certainly no proof whatever that they are cases of typhoid fever. I think that, with very little chance of mistake, these cases can be recognized as distinct, clinically, from our usual cases of typhoid. Of course, I should not be at all surprised if further investigation, especially bacteriological investigation, should prove these cases to be identical, as to their origin, with typhoid fever; but if they are, I still think that the desire to separate them as a clinical form is not amiss, in view of the bearing upon treatment.

CREASOTE IN TUBERCULOSIS PULMONUM.

By J. T. WHITTAKER, M.D.,
OF CINCINNATI.

In the presentation of a paper to one of our societies we are not allowed the liberty of even our immediate forefathers. We are compelled to entirely eliminate the "personal equation," whereby the matter becomes more, perhaps, exact, but often less interesting. This fact is illustrated in one of the earliest contributions "On the Medicinal Properties of Creasote," which the author, John Elliotson, M.D., F.R.S., President of the Society, read at the opening of the Society's Apartments, February 24, 1835, quoting the remark of Lord Bacon, that physicians apply themselves too exclusively to general indications, neglecting the peculiar properties of remedies in particular diseases. Bacon says: "They merely go on in their prescriptions, *addendo, et demendo, et mutando . . . . quid pro quo substituendo,*" and he advises that some physician of education and practical knowledge shall devote some time to the exhibition of medicines in particular diseases.

Elliotson says Bishop Berkeley killed creasote by over-praise, just as Pope killed Berkeley when he said:

> "Manners with candour are to Benson given,
> To Berkeley every virtue under heaven."

Elliotson tried creasote in this paper, in phthisis and epilepsy, and discovered the virtue of it in obstinate vomiting. He says: "While I was trying creasote in phthisis and epilepsy, Asiatic cholera became epidemic in London. Two cases occurred at St. Thomas's, and creasote was given with the effect of immediately arresting the vomiting." The author saw no benefit from creasote administered internally in the treatment of phthisis, but found it of great value when used by inhalation. Thus: "I am satisfied that it is no remedy for tubercles. Where, however, only a single ulcer, or but a small number, exist in

the lungs, and there is no disposition to further tubercular formation, it is very beneficial." A young gentleman, with a large solitary cavity in his left lung, has completely recovered, and not the slightest morbid condition is discoverable by the ear. He knew the case of a lady who steadily augmented her dose of creasote to forty drops before it disagreed. All this was in 1835, only three years after creasote was discovered. Disregarding now the literature of tar, forms of which were recommended in phthisis as long ago as 1817, by Sir A. Crichton, physician to the Empress of Russia, and by Morton, of Philadelphia, as early as 1834, as a treatment "with which nothing could compare," we come to creasote, the essential ingredient of tar.

Creasote, κρέας, flesh; Attic, κρέως; Doric, κρῆς, hence creasote, creosote or cresote, σώζειν, to save, was separated by Reichenbach, of Blankso, in 1832, from wood tar, and received its name from the property of preserving meat from decomposition without rendering it unfit for nutrition. Two years later Runge extracted carbolic acid from coal tar. Gerhardt gave this product the name phenol. The substances were confounded until 1853, when Gorup-Besanez declared that the creasote extracted by Reichenbach from beechwood tar was an entirely different body from carbolic acid, in that creasote consisted of a mixture of guaiacol and creasol; while carbolic acid is crystalline and contains but one atom of oxygen; hence it is not really an acid, but an alcohol, and should be known as phenyl-alcohol. Creasote is the cause of conservation of meat in smoking. A piece of fresh meat allowed to remain half to one hour in creasote water takes the smell and taste of smoked flesh, and withstands decomposition absolutely. Insects and fish perish at once in creasote water, and plants watered with it wither away. According to Miguet, a young and vigorous rose bush in full bloom, thus treated, perished in the course of eight days. A few drops of the same solution applied to a red rose, deprived it both of color and life. (Stillé.)

The toxic effect of creasote is, however, much less than that of carbolic acid. In a case reported by Pereira, a fatal dose was 120 drops, diluted with double the quantity of water. According to Taylor, 90 drops, well diluted with water, may be taken safely. The experiments by Husemann and Ummethum showed that it required, by subcutaneous injection, five times as much creasote as carbolic acid to kill frogs, and more than twice as much to kill pigeons. In rabbits, one gramme

constitutes a fatal dose of carbolic acid. This quantity of creasote produces in the rabbit no symptoms at all, and death occurs only after the exhibition of four grammes.

The virtue of creasote depends upon its purity, especially upon its freedom from carbolic acid and pyrogallol. According to Vigier, creasote owes its effect not to any single chemically defined substance, but to a mixture of creasol, especially to guaiacol, also to derivatives of pyrogallol, which last substance is toxic. Guaiacol, which is the active principle of creasote, according to Picot, Lepine, and others, is more readily tolerated than creasote, but it is seldom found pure in commerce. Impure creasote, that which contains carbolic acid, irritates the mucous membrane of the stomach and intestines, and produces local inflammation. Some of the contradictory testimony regarding the remedy is thus explained.

The uncertainty of the drug in former, and even in recent use, is illustrated in the statement by Oertel (*Handbuch der allgemeine Therapie*, 1882), that creasote acts like carbolic acid, but as the composition of creasote is so uncertain, it is better substituted by carbolic acid. Dagivait, indeed, maintains that failures are due to impurities. He published a communication on "Impure Creasote the Cause of Failure in the Treatment of Pulmonary Tuberculosis."

In a healthy man therapeutic doses produce no action whatever on the circulation, nutrition, colorification. The proportion of urea, of phosphoric acid in the urine, remains the same. The uric acid only diminishes. Once absorbed in the body, creasote escapes chiefly by the lungs and the kidneys, and there is observed in cases of the absorption of toxic doses, polyuria, dysuria, brown discoloration of the urine, bronchial excitation with hyperæmia, and the impregnation of the breath with creasote. The taste is preserved in the mouth in certain cases, which seems to prove that creasote is eliminated also by the salivary glands.

Bouchard found that it required seventeen ccm. creasote per kilogramme to kill a rabbit. By injections, subcutaneous, of an oleaginous solution of creasote, it required a dose nineteen times as strong. One may, without danger, inject every day in a rabbit twenty-five ccm. per kilogramme in an oleaginous solution. This daily dose, which is without danger to an animal, is equivalent to 15 grammes to a man weighing 60 kilogrammes, *i. e.*, ℥ss to 140 pounds. A non-fatal dose

produces as a sole phenomenon in animals a retardation of respiration. The number falls from 80 to 16 in the minute. Long and anxious pauses occur. Bouchard first remarked upon this retardation of respiration in man.

Forty-five years had elapsed since the discovery of creasote. The drug was widely, almost wildly, used, and then forgotten. From this oblivion it was rescued, in 1877, by Bouchard and Gimbert, the real pioneers in this therapy, who ascribed to it great virtue in the treatment of phthisis.

Sommerbrodt has just published a statistical essay of the use of creasote since 1887 in chronological order, showing the gradual development in creasote therapy. The most remarkable result is the increase in the daily dose, and the author confirms the statement originally expressed, that the more creasote is tolerated during the day the better is its effect. While the daily dose for an adult in former years reached a maximum of ½ gramme, in later times the dose has been gradually increased to 4, even to 8 grammes per day (in children ½ to 1½ grammes), not only without injury, but with the best effect. Cough and expectoration disappear. The undesirable use of morphia is rendered superfluous. Night sweats cease; the appetite becomes sometimes enormous; the body-weight gains. The local effects in the lungs disappear, or remain only as relics. Even in the grave, apparently hopeless cases, remarkable, though, of course, only temporary results are accomplished. While the author formerly "in small doses saw only essential improvement, later, with large doses, he has been able to accomplish cures, and that, too, not only in lung tuberculosis, but also in surgical tuberculosis, and in scrofula." The increase in the consumption of the drug may be appreciated by the statement that in the Moabit the quantity used in 1877 was 1 kgrm. 50 grm.; in 1888, 4.225 kgrm.; in 1891, 11.7 kgrm., and in 1892, 18 kgrm., *i. e.*, about 40 pounds.

On the other hand, Fürbringer declares that he has not given creasote in the last one or two years, because he had not obtained success enough to justify it. "In half of the cases there was no influence either favorable or unfavorable; in one-fourth of the cases the influence was directly injurious. The remedy hurt the stomach. Patients lost appetite and became miserable." The rest experienced various subjective and objective effects, but when these apparent results of crea-

sote were compared with hygienic or dietetic procedures without creasote, there was no difference to record.

May these diametrically opposite opinions of good clinicians be reconciled in the study of the action of the drug.

Guttman found that in solution of 1 : 4000 creasote exercised a marked inhibitory faculty on the growth of tubercle bacilli, and in solution of 1 : 2000 actually destroyed it. Guttman's experiments were made in 1887 out of the body, but deductions could not be drawn thence in the body because the concentrations were too great. In order to secure a proportion of 1 : 4000, a concentration which hinders the growth of tubercle bacilli, more than 1 gramme of creasote would have to circulate in the blood.

Cornet showed that large quantities of creasote in the stomach did not prevent the development of the tubercle bacillus in guinea-pigs. In the proportion of 1 : 100 it fails, after twenty hours' exposure, to destroy tubercle bacilli in sputum. A saturated aqueous solution does not destroy the tubercle bacillus in cultures in twelve hours. (Sternberg.)

In Trudeau's experiments, rabbits inoculated with tuberculosis, and treated with creasote subcutaneously, presented the same lesions as control animals not so treated.

Bouchard deduced from his experiments that 3.50 grammes, about 1 drachm, of creasote would suffice to destroy bacilli in the middle of the body of a man weighing 60 kilos, 140 pounds, but Burlureaux injected into tuberculous patients as much as 40 grammes of creasote a day. Now, according to Bouchard, all these bacilli ought to have been killed and the patient ought to have recovered. But these results did not occur.

Albu's experiments show that tuberculous sputum taken from bodies saturated with creasote maintains its virulence. He injected such sputum in the anterior chamber of the eyes of rabbits. The course of the disease was perfectly typical. By the nineteenth day tubercle bacilli formed their first colonies visible under the lens. Subsequent changes ensued in course. Only one animal showed miliary tuberculosis.

In a second series of experiments, such sputum was injected into guinea-pigs, intra-peritoneal. The peritoneum showed virulent material in six weeks. Hence, there is no specific influence of the drug.

The clinical proof of the effect of the remedy in tuberculosis is the influence on the fever. Creasote has no real influence on the fever. The writer has tested this fact in every way. Though the patient be saturated with the drug by every avenue—by the stomach, by the lungs, by the bowels, by the skin, by all these methods at once—creasote does not control the fever. Thus, there is no specific influence, and no real, that is no radical, or no direct cure. But if creasote can cure indirectly, or if it will only relieve complications, it will hold its place in therapy until something better is found. Sommerbrodt says that though a scientific explanation is still lacking, he believes that creasote alters the tissue of the cells and the chemical condition of the juices of the body, so that they no longer furnish a suitable culture-soil for the tubercle bacilli, the colonies of which will not grow in it.

Ludwig maintains that creasote destroys the toxine of the tubercle bacillus. This is a fine theory, but undemonstrable at present. After the injections, catarrhal forms of the apices will show no bacilli. The caseous will soon assume the mucoid form, which seems to exercise a toxic effect on the microbe.

According to Peter, injections of guaiacol and creasote act by substituting a fugitive and curable hyperæmia for a tuberculosis hyperæmia. Under the drug, cough and expectoration diminish; fever and night sweats cease; appetite returns, and the patient gains weight and strength. The benefit is due to its elimination by the lungs. It excites a simple and transitory inflammation, which substitutes a specific catarrh.

Dujardin-Beaumetz, indeed, declares that creasote in appreciable dose congests the bronchial mucous membrane and promotes hemorrhage, while Guiter claims that creasote acts as an irritant which favors cicatricial sclerosis. Finally, Peter believes that creasote is more useful in protecting healthy tissues than in curing those which are already invaded. All these views are theories undemonstratable by clinical proof.

Creasote acts also on the stomach, as has been observed by Walche, Hopmann, and Klemper. It excites the appetite and lessens the distress of indigestion. In fact, this action is the first observed. Most patients improve decidedly for a time under the immediate change of nutrition. And this action is well understood. For, according to Brunton, while one part of chlorine in 8540 parts of a saturated solu-

tion will arrest the digestive action of ptyalin upon starch paste, and corrosive sublimate is so enormously destructive as to arrest its action even in one part to 51,000, creasote has no action on ptyalin, even in saturated solution, and has but a very feeble action upon pepsin.

It is impossible to proceed further in the study of the action of a remedy in tuberculosis without more definite knowledge of the nature of tuberculosis and what it is that is to be accomplished. In this regard there is new, or at least, more definite knowledge. It is known now that the whole character of consumption, *i. e.*, tuberculosis pulmonum, was not determined with the discovery of the bacillus tuberculosis. This is the keystone, it is true, but there are other stones nearly as important, which go to make up the structure. It is now known that tuberculosis of the lungs, at least, is not a pure process. In test-tubes, a culture, to be kept pure, must be secluded from the outside air as a *sine qua non*. This seclusion does not obtain in the lungs. On the contrary, the tubes containing the cultures, *i. e.*, the bronchial tubes, are all open to the air, and are subject to constant contamination. So that human differs essentially from laboratory tuberculosis.

The contaminating bacteria of sputum have been recently investigated by Evans and Babes. Maragliano called attention to the possibility of their clinical signification, as did also Czaplewski, Ziegler, and Thorner. Long ago, Koch in his work, and after him Gaffky, encountered the tetragonus as an occasional associate of the tubercle bacillus, and spoke of its pathogenic properties.

Cornet, on *Mixed Infection*, says it is well known to every one who has experimented with tuberculous sputum in animals, that many of the inoculated animals, especially rabbits, often perish in a few days from septic processes. For years, in his experiments, he avoided the sputum of phthisis florida, and selected rather that of chronic cases, because experience taught him that such sputum rarely causes death by accidental disease. In one case described with acute exacerbation, there was found in the sputum, besides the tubercle bacillus, partly isolated and partly abundant diplo- and streptococci. Cultivation on agar gave almost a pure culture of streptococcus colonies. On post-mortem, microscopic sections showed, especially in the walls of the cavities and caseous parts, streptococci and monococci thickly sown. In agar, developed innumerable streptococcus colonies, like those found in sputum, and besides, but in less number, perhaps in the relation of

one to twenty, the staphylococcus and pyogenes aureus. The streptococci grew in bouillon in firm masses, and long chains, without making the fluid opaque, a property, according to v. Lingelsheim, peculiar to pathogenic streptococci. They resemble in form and growth the streptococcus described by Curt as streptococcus agglomeratus. A mouse inoculated, died in three days. The same streptococci were obtained from the blood of the heart, liver, and lungs in pure culture. A rabbit and a guinea-pig injected, died, both in twelve days. Their organs were filled with streptococci.

Of the twenty cases investigated post-mortem, and so far as possible, *intra vitam*, there occurred twelve times such a dominating presence of streptococci that its work in the production of symptoms could not be questioned. Petruschky confirms this fact. He found the streptococcus dominant in the great majority of cases studied. In eight of fourteen cases, streptococci were found in the blood and juices of all the organs, whereby the significance of streptococcus infection is sufficiently shown. Pasquale also demonstrated streptococci in various tuberculous processes from the dead body. Therefore, the expression "mixed infection," is not exactly correct, because it is not a case of simultaneous invasion. It is rather a secondary invasion of streptococci, that is, it is properly a wound infection, and should be characterized as "a secondary infection." The inundation of the whole body with streptococci induces septicæmia. Hectic fever is distinguished by its morning remissions, by its more or less sudden evening elevation. It is the fever of erysipelas, acute, suppurative processes, puerperal fever, produced by pyogenic cocci, in the great majority of cases by the streptococcus Koch calls this see-saw record the "streptococcus curve."

Can it be that creasote is destructive to these associated micro-organisms?

Upon this subject there is less definite knowledge.

Marfan declares that creasote has an action more energetic on the micro organisms of secondary infection than on the bacillus itself. From this point of view it is, he says, "the most puissant of the balsams." Under its influence, the cough diminishes, the expectoration and the râles become less abundant.

Sternberg found creasote fatal to micrococci in general in the proportion of 1 to 200.

Creasote was found by Werneke to destroy yeast in a dilution of 1 part to 500 of water, and by Bucholtz, to kill ordinary bacteria in a dilution of 1 part to 1000 of water. This difference, according to Brunton, enables us to arrest fermentation in the stomach, depending upon the presence of low organisms, while the digestive action of pepsin is not, or is only very slightly disturbed. (Brunton.)

It is not likely that creasote neutralizes or destroys the streptococcus itself, because it shows no real effect upon the fever. But it certainly does inhibit the growth, or actually destroys some of the organisms which induce fermentation in the stomach and intestine, without interfering with the actual processes of digestion, and this is the actual knowledge in hand at the present time regarding the action of the drug. Thus creasote contributes to the cure of consumption as does arsenic, hydrochloric acid, benzoate of soda, etc., through the avenue of nutrition.

In proof of the fact that the remedy acts only symptomatically, Albu cites an instructive case. A fifty-three year old laborer was received on the 11th of November. The first time he was treated with tuberculin; the second time on the expectant plan; the third time with creasote. Each time he regained the ten or twelve pounds which he had lost outside of the hospital. This influence is to be ascribed only to the improved hygiene of the hospital.

Creasote is best given in gelatin capsules, 0.1 creasote, with cod-liver oil. Pure creasote is cheaper. Sommerbrodt uses the preparation of Hartmann and Hauers, of Hanover. It may be given in mixture of two parts of tincture of gentian in milk or wine. It should never be taken on an empty stomach, best immediately after the three chief meals. It never hurts the stomach. It increases menstruation, consequently it should be checked during that period. It may be continued for years, and must be continued long after apparent cure. It is, of course, much assisted by climate, altitude, lung gymnastics, good nourishment, but it does good even under the most unfavorable surroundings.

Vopelius declares that the more creasote is tolerated, the better is the effect. He gave it in does up to the point of tolerance, and found the improvement in correspondence. The appetite increased, and with it the weight. He gives it uniformly, beginning with a daily dose of 2 grammes, and increasing it up to 4, 5, 6, and 8 grammes a

day. He gives it altogether with tincture of gentian in equal parts, with great abundance of milk as an emulsion. In shaking it about with milk it becomes so finely subdivided that it no longer burns or irritates the mucous membrane; on the contrary, it rather stimulates the stomach to secretion. He gave it also in tuberculosis of the bones and joints in connection with local treatment.

The remedy has been administered by the stomach, by the rectum, by inhalation, and by the skin. In the rectum it has been given systematically by Revillet according to the following formula:

Water, 200 grammes; creasote pure, 2-4 grammes; oil of sweet almond, 25 grammes; yellow of egg, 1. The creasote is first dissolved in the oil, and subsequently emulsified with the yellow of egg. This produces a liquid, homogeneous, of the appearance of milk, and of a yellow color. The emulsion may be made still finer by the addition of some gum. The oil of sweet almond is preferred, because it does not produce colic, and because it contains besides matters which act as an adjuvant in the alimentation. The injection is taken preferably in the evening, as it is best retained at night. After injection, the signs of absorption show themselves rapidly. The patient instantly experiences the taste of creasote in the mouth, and the urine may assume a greenish-black color.

Creasote was injected through the thorax walls into the apices of the lungs by Lepine and Truc, of Lyons, and Gougenheim, of Paris, without any particular result.

The first idea of subcutaneous injection was entertained by Bouchard in 1875. Du Castel, in 1882, injected a peptonized creasote subcutaneously, but the introduction of the treatment is really due to Gimbert, in 1886. He was soon followed by Burloureaux. Gimbert injected a solution of creasote 1 gramme to 14 grammes of the oil of sweet almond, drop by drop, stopping occasionally to avoid pain. Gimbert injected only 15-22 grammes of the creasotized oil, that is to say, 1 to 1.50 of creasote. Burloureaux injected on the average 50 grammes, *i. e.*, over an ounce and a half a day, and he even passed this dose, and made daily injections of 100, 180, 200, and even 220 grammes in order to saturate the organism. The remedy is really harmless.

According to Burloureaux, who treated 400 patients in this way, where tolerance ceases, the prognosis is sombre, and the patients are

lost. If the patient perceives the taste of creasote a long time, if his urine becomes black, if he has vertigo, torpor, and sweats, recovery is despaired of. Sweating frequently occurs at the beginning of treatment, sometimes immediately in consequence of the injection. It is occasionally profuse, and may last seven or eight hours. It has no great significance, and does not indicate intolerance. It is rare that it occurs alone; more often it is accompanied by fever, sometimes by chill, with headache and coldness. The extremities may become icy cold. It is the picture of the algid form of pernicious fever. It does not last longer than three-quarters of an hour, and is followed by a state of *bien-être*. The dose in these cases is excessive, and should be reduced.

Frey declares that the drug is not so effective when administered by the mouth, or the rectum, as by the skin, absorption from which is very rapid. The taste is perceived in a few minutes after administration, and the odor is noticed in the breath. Injections are almost painless. Large quantities, however, produce thickening of the skin, and prevent absorption. Frey begins with olive oil, sterilized, 15 grammes; creasote, 1 gramme; injected at first 3 grammes, later up to 10, three times a day, and continues two or three months, after which he uses a solution of 1 in 9. The injection should be entered slowly, in the time of about a minute. The most preferable site is the back, the inter-scapular region, or the thorax.

The best results are reported in scrofula and local tuberculosis, that is, in precisely the cases where other therapy is most efficacious. This is a typical case: A patient who had been treated surgically for tuberculosis of the manubrium sterni and the internal extremity of both clavicles, was put under the creasote treatment for a voluminous suppurating adenitis of the neck. In 25 days he received 1800 grammes of creasotized oil, by the skin, and 1000 grammes by the rectum. He increased in weight seven pounds; suppuration disappeared; the adenitis receded, and the patient recovered.

Another case: A patient absorbed by the skin ten pounds of creasotized oil, and by the bowel over two pounds in five months, and was cured of tuberculosis of the testicles.

In estimating the value of a remedy in tuberculosis pulmonum, we must remember how deceptive is the prognosis of the disease. Thus, there was the Baron Cloquet, affected with tuberculosis of the lungs

at thirty-two years, and given six months to live, not more, after a consultation with Andral, Chomel, and Louis. Nevertheless, he lived more than fifty years afterward, and attended the funeral of all three of his prognosticators. It must be remembered that he lived under exceptional conditions. A spiritual egotist, he passed seven to eight months of the year in the Midi, on a splendid property which he possessed, with abundant nourishment, but delicate, that his stomach was able to digest easily. *En outre,* he never had the least fever. (Peter.)

Considered only from a clinical standpoint, creasote holds its place. It is an easy routine practice, and it is really, as shown, perfectly harmless in any dose. In my wards at the Good Samaritan Hospital all the tuberculous patients are put upon creasote immediately upon entry. We begin with five drops of a mixture of creasote and tincture of nux vomica, or where strychnia is contra-indicated, tincture of gentian, in a teaspoonful of whiskey and a tablespoonful of water three times a day after meals, increase the dose a drop daily to ten, whereupon additional doses are given at 10 A.M., 4 P.M., and at bedtime, as before. The body shows signs of saturation at 60 drops per day. Six cases were treated also hypodermatically with the same dosage, but without any appreciable advantage over the internal treatment alone. Four bad cases with marked hectic, and forty lighter cases without hectic, were treated, in addition to inhalations in the pneumatic cabinet, and this or a similar method has been tried thoroughly in France; but, aside from the psychical effect, with no additional benefit.

All our cases in non-febrile periods are treated with tuberculin, which remains the only radical address to pure tuberculosis, but which has no or only a bad effect upon septicæmia.

Conclusions:

1. Creasote when pure is harmless.
2. It has no direct action upon the tubercle bacillus.
3. Tuberculosis pulmonum is chiefly a secondary infection by a streptococcus.
4. Creasote has no direct action upon this streptococcus; hence none whatever upon hectic fever.

5. It destroys lower organisms, especially those which produce fermentation, without affecting the process of digestion.

6. Hence the virtue of creasote, which is undeniable, is chiefly but not wholly upon nutrition.

DISCUSSION.

DR. WOOD: I rise with a good deal of hesitancy to speak on this subject, because recently in the University, in Philadelphia, one of our bacteriological professors told me I was too old to sympathize with modern medicine; therefore, I speak with great reluctancy and becoming modesty. It seems to me that in the rage of bacteriological study physicians are often forgetting that they ought to treat the individual sometimes, and not the bacteria. Some years ago, as we all know, every phthisical patient was dosed with sulphuretted hydrogen. The result was at first said to be very extraordinary, but in a few months all the syringes and sulphuretted-hydrogen squirts in general were relegated to the past. Creasote, it seems to me, is running very much through the same history. I have no doubt that sulphuretted hydrogen and creasote are valuable remedies, but I do not believe that either of them acts in any way specifically upon the bacillus. I have seen cases of chronic bronchitis of a very severe type, which failed to improve under any other treatment that I could think of, get well rapidly under the use of sulphuretted hydrogen. I have seen the same thing from the use of creasote in similar cases, and I believe that in certain conditions of secondary catarrh in phthisis, sulphuretted hydrogen and creasote are valuable remedies—not by any action in disinfecting the lung, but by their action on the individual who is the unfortunate host of the parasite.

DR. TRUDEAU: I have but little to say in comment upon this paper, but will say that the tubercle bacillus bears cheerfully a good deal of medication that is disastrous to its host. It is my experience in animal tuberculosis that no matter how large the doses of creasote injected, the disease develops regularly in its natural course. It seems to me that in phthisis it does good in improving the condition of the stomach and intestinal canal, and I have not quite discontinued its use. It is like arsenic, if it improves the appetite and digestion it is well to keep it up; but if it disagrees with the stomach, it should be omitted. It is in no sense a specific.

DR. BOND: Dr. Whittaker has told us that he uses strychnia with the creasote, but he does not say what part the strychnia plays in producing beneficial results. Dr. Wood, I think, has given us the key to this whole matter of treatment. It is an observation made by most doctors, that patients

very often recover from these conditions when active out-door exercise is employed, or when a change of climate is made, especially to higher altitudes, as Denver, Col. I think that the conclusion growing out of this whole matter is that there are a great many things that are beneficial to the individual which must in the end tend to counteract the influence of forces from without, whether due to one cause or a number of causes.

DR. WHITTAKER: The criticisms are so strictly in accordance with what I have said, that there is nothing to explain or contradict.

THE INTESTINAL ORIGIN OF CHLOROSIS.

BY F. FORCHHEIMER, M.D.,
OF CINCINNATI.

THE object of this paper is to show that chlorosis is produced by changes that take place primarily in the small intestine. Sir Andrew Clark in an excellent paper on "The Anæmia and Chlorosis of Girls, Occurring More Commonly Between the Advent of Menstruation and the Consummation of Womanhood" (*The Lancet*, Nov. 19, 1887) and indirectly Bunge, Landwehr and Kobert (*St. Petersburg, Med. Wochenschrift*, 1891), have called attention to the connection between intestinal processes and chlorosis, so that the fact has been admitted that such connection exists. The following may go to show how chlorosis originates in the intestine:

The characteristic blood condition of chlorosis is oligochromæmia: a diminution of Hb. for each red corpuscle without even approximately great diminution in the number of red corpuscles. It is unnecessary to add that a clinical diagnosis could not be established from blood examination alone; that oligochromæmia occurs as a physiological condition, or that some individuals apparently in the best of health are oligochromæmic. Accordingly, oligochromæmia would bear the same relation to chlorosis that glycosuria does to diabetes mellitus.

A diminution in Hb. can occur from two causes only: either the destruction of Hb. becomes abnormally great or the formation becomes abnormally small. As far as we know, destruction of Hb. is always associated with destruction of the red corpuscle; our definition of chlorosis, then, would preclude the possibility of this disease being due to destruction of Hb. But let us admit that a separate destruction of Hb. and red corpuscle can exist, a condition hinted at

by many authors, it will then become necessary to prove that, commonly, at least, this does not occur in chlorosis.

The formation of the stroma and the Hb. of the red corpuscle consists of two distinct acts, as is proven by their first appearance in the mesoblast during fœtal life, and in extra-uterine life by the behavior of the erythoblasts of Bizzozero. We have first the stroma and then the coloring matter, and, therefore, it is not unreasonable to suppose that normal (numerically) cell formation might go on with diminished Hb. production (chlorosis) or normal Hb. formation with diminished corpuscular production, either process causing a diseased condition

That there is no appreciable destruction of Hb. in chlorosis can be proven by an examination of the urine in all cases in which the Hb. sinks to 60 per cent. or below (Fleischl's hæmometer). My attention was first called to this fact by a routine urinalysis in the case of a Russian girl, when the so-called urophæin test of Heller was followed by a negative reaction. In this girl, a characteristic imported case of chlorosis with Hb. 40 per cent. and red corpuscles, 3,975,000, the urine was found as usually described, "copious, pale, acid, of low density, somewhat deficient in urea, and always prone to speedy decomposition" (Clark). As the urophæin test is supposed to be produced by all the coloring matters of the urine except the urine-indican, it became necessary to determine whether urobilin was present or not. A chloroform extract, treated with iodine and dilute potassium hydrate gave no fluorescence (Gerhardt's test) and, practically, no green color, so that, when this examination had been repeatedly made, the conclusion could not but be formed that urobilin was practically absent. As urobilin is one of the end products of bilirubin, and the quantity of bilirubin depends upon the destruction of the red corpuscles or their Hb., it would seem to follow either that there is failure of absorption of hydrobilirubin from the intestine or lack of formation. There is no diminution in the absorptive function of the small intestine, so that there must be less Hb. destroyed than normal. The fact must be mentioned that in chlorosis of less degree there is not always an absence of urobilin. This can be explained by taking into consideration the quantity of Hb.; with the destruction of an equal number of red corpuscles, it is sufficient at times to produce the urobilin reaction, but not always. The statement can be made, then, that chlorosis is not due to hæmolysis

either of corpuscles or the Hb. but must be due to faulty hæmopoiesis, as far as Hb. is concerned, and, possibly in severe cases, secondarily even as to red corpuscles.

Little has been done on the origin of Hb. It has been known for some time that after a full meal the amount of Hb. sinks, but this can be satisfactorily explained by the dilution of blood due to absorption of fluid. From an experimental therapeutic standpoint much has been done; but the results are so variable that they may be called inconclusive. It would seem a simple matter to prove or disprove the absorption of iron or iron-containing-albumins from the intestine, yet, with the technical difficulties and the incomplete establishment of physiological data this has not been the case, so that it became necessary to make a series of experiments which had reference to Hb. only. In these, the question of iron-absorption or excretion, or the conversions of Hb. could be abstracted from entirely, and direct comparative observations of Hb. could be made. The object of the first series was to determine whether Hb. was formed in the intestine, having previously had conclusive evidence that Hb. formation could be increased by the introduction of certain substances not containing iron into the intestine of patients. Rabbits were chosen for the observations, purely for the purpose of convenience; during full intestinal digestion they were put upon the rabbit holder, the abdominal cavity was opened, and blood was examined from the terminal branch of the mesenteric artery and its accompanying beginning of the mesenteric vein. Care was taken to open the bloodvessels as near as possible to the entrance or exit, so that arterial blood was examined immediately before it went into the capillaries of the intestine, and venous blood directly it came from them. As the result of forty observations, the average is as follows:

In the artery: Red corpuscles, 5,362,000. Hb., 78¾ per cent.

In the vein: Red corpuscles, 4,546,000. Hb., 78¾ per cent.

From which we deduce as follows: the number of red corpuscles is dimished in the veins, while the quantity of Hb. remains the same; therefore Hb. is absolutely increased in the vein and each red corpuscle carries more Hb. in the vein than in the artery. The dilution of venous blood during digestion must be taken into consideration. This would, probably, also account for the diminution of red corpuscles. If the blood contains 78¾ per cent. Hb. before going through

the capillary circulation, takes up fluid there, and comes into the veins containing 78¾ per cent, it certainly follows that Hb. is increased in the vein. As a result of calculation it will be seen that each red corpuscle carries about 18 per cent. more of Hb. in the vein than in the artery. The only other explanation that the quantity of Hb. remains stationary in the arteries and veins can therefore be rejected.

From this observation the conclusion can be drawn that, in the rabbit Hb. is taken up by the blood from the intestine and that it must be formed either in the parts supplied by the arteries, *i. e.*, the mucous membrane in its broadest sense, or within the lumen of the intestinal canal. It does not seem to be going too far to extend this view to the human being when corroborated by other testimony.

It has been stated that the quantity of Hb. is diminished after a full meal; but, to my knowledge, no investigation has been made as to the influence of intestinal digestion upon Hb.-formation. It was necessary, therefore, to examine the blood at this time in order to determine whether the view expressed before could apply to the human being. Fifteen adults whose histories were known were examined in the following way: the blood was examined before they sat down to the heaviest meal of the day and from three to four hours afterward, with the following average result as to red corpuscles and Hb. In all cases but one there was a decided increase in the number of red corpuscles and in Hb. Before the meal Hb. was present as 86 per cent. and red corpuscles as 4,905,000; after the meal Hb. 87 per cent. and red corpuscles 5,044,000, so that there was an absolute increase of Hb. of nearly 3 per cent and a slight increase in Hb. for each red corpuscle after the meal (represented by the fraction $\frac{2861}{4{,}905{,}000 \times 5{,}044{,}000}$). It will be seen, then, that a large quantity of Hb. is added to the circulation during intestinal digestion and that the number of red corpuscles is increased, so that, although the simple experiment of the rabbit cannot be carried out upon the human being, its results can be fully applied to the latter.

A very practical result of these examinations is, that for comparative observations upon the same individual the examination must always be made at the same time of the day and in approximately the same relation to a meal. This has been done in all the examinations to be reported upon further on.

It now having become apparent that Hb. was formed in the intestine, and that this lack of formation could be looked upon as the cause of chlorosis, it seemed feasible to attempt a solution of the problem why Hb. was not formed in sufficient quantity in this disease. Two ways were open: first, by means of therapeutic attempts, and secondly, by direct investigation; the former the easier of the two, but to be referred to later.

Three litres of urine, with the following general characteristics, were taken from a chlorotic patient: acid reaction, sp. gr. 1012, pale color, indican increased, urophæin diminished, urobilin test negative, no albumin, no sugar. After having been filtered there was added three times the quantity of alcohol, drop by drop, which was followed by the production of a flocculent, not very copious precipitate; this was put through a filter. The process of filtration was very slow, taking fully forty-eight hours, and when the attempt was made to redissolve the precipitate in distilled water it was found impossible to do so. The substance was then obtained by drying upon the filter. In order to find out whether it had toxic properties, a small quantity was rubbed up in water and injected into the subcutaneous tissue of a rabbit. In small doses it produced elevation of temperature, apathy, loss of appetite and loss of muscular power; in large doses, the following symptoms were noticed, the rabbits dying about eleven hours after injection. First, about three quarters of an hour after the injection, rapid elevation of temperature (103½° F.) and with this, loss of motion. About an hour after the injection, temperature begins to fall, until just before death it falls to 91° F. After two hours the animal becomes absolutely motionless, reacting only upon strong stimuli, to be followed by convulsive movements. The post-mortem examination reveals no evidence of inflammation, the internal organs seem normal with the exception of the lungs and kidneys, both being very much congested. The veins and the arteries contain fluid blood, and there is no evidence of clotting anywhere, except in the heart.

The toxicity of this substance being established, an attempt was now made to determine its nature, especially in view of the fact that normal urine is supposed to contain a toxic body (urotoxin). That it is an albumin was proven by the biuret, Millon's and xanthoprotein tests. Peptones and albumoses (except heteroalbumoses) were excluded on account of insolubility in water. The toxalbumins could be excluded on account of dissimilarity of animal reaction. The body is soluble in NaCl and precipitated by saturation; it is

precipitated by $(H_4N)_2SO_4$; it is precipitated, like a globulin, by CO_2, so that, in all probability, we are dealing with a double body, a proteose, of toxic properties, the exact nature of which will have to be determined by further investigation.

As to its origin, the statement can be made with a certain amount of certainty: it is an intermediate product between albumin and peptone, which is produced either by putrefaction or digestion in the small intestine, possibly both. It is not improbable that this body is the result of a process which destroys the albumin part of the molecule of the precursor of Hb. What form this is in it is too early to determine, although Bunge's hæmatogen-organic iron found in the yolk of eggs is claimed by the discoverer to be destroyed in the intestine by H_2S, just as we imagine the precursor of Hb. to be destroyed in the intestine of chlorotic patients by some active body, either some lower form of life or some enzym, the result being the poisonous body in the circulation, and prevention of Hb.-formation.

Lastly, I wish to present briefly, the therapeutic evidences I have gathered. Sir Andrew Clark states in his paper that "if, in the treatment of this malady, I were perforce limited to the employment of one sort of drug, the drug which I should choose for use would be an aperient." In the eleven cases from which I shall draw my conclusions I have used neither iron nor aperients, but have salol or hydro-naphthol (so-called). It will be readily understood why the number of cases is so small when the statement is made that chlorosis of high grade is not very common with us, and that all the cases which I have seen have not been exclusively treated by these drugs. The object of the method was to introduce some substance into the small intestine, so as to prevent abnormal decomposition, and none better suggested themselves than salol, with its salicylic acid, at first, and latterly hydro-naphthol.

In order to make the therapeutic tests as pure as possible, no laxatives were administered, but the bowels were emptied by means of agents acting upon the large intestine only (enemata, flushing the large intestine, or glycerin, either as an injection or suppository.) The eleven cases were all females, varying in age from 15 to 35 years; menstrual difficulties were present in seven cases—the most pronounced case claiming to be regular in every respect; constipation was present in six cases, stomach trouble in four. In all the

cases the urine presented the chemical characteristics mentioned before. Two of the cases were chronic chlorosis, one of which was cured after a long siege, the other one presenting relapses, so that she cannot be reported as cured. The quantity of Hb. varied at the beginning from 40 to 70 per cent. and the number of red corpuscles from 3,766,000 to about the normal for women. Six of the cases were treated with salol, five with hydro-naphthol, and one with both. The patients were kept under treatment until Hb. reached 90° per cent or over, and the time of treatment varied from five weeks, as the shortest, to three years in the one case. All precautions were taken to establish accuracy in blood examination (counting a sufficient number of squares in the hæmocytometer, the arrangement of the light for the hæmometer, examination at the same time of day and with reference to meals, etc.).

The results, expressed in general terms, were steady increase in Hb. interrupted by regular diminution as the result of menstruation and several other causes. The smallest amount gained in one week was 5 per cent., the greatest 20 per cent., when a gain was made. In one patient, the only exception, it took two weeks before the remedy (salol) produced any effect, but in two weeks after that the Hb. had risen from 65 per cent. to 85 per cent. With the rise in Hb. all the patients began to improve, the nearer 80 per cent. the more the symptoms began to disappear, and from ordinary examination, without blood test, most of the patients would have been willing at this point to have been discharged as cured. In the obstinate, chronic case referred to above, the Hb. was just as surely increased as in the others, but, as soon as treatment was stopped the Hb. would again sink, so that after the end of two or three months the patient would present herself again with Hb. 55 or 60 per cent. In no way, however, could she be looked upon as disproving the effect of these two remedies upon Hb.-formation. Hydro-naphthol seemed, upon the whole, more efficacious that salol, the results being more quickly obtained and the rise being more rapid.

If any deduction could be drawn from the different action of the drugs, it would be that salol acts both upon lower forms of life and upon enzyms, while hydro-naphthol probably acts only upon the former. However this may be, both act by causing increase of Hb.,

the salol acting, in addition, especially in the direction of producing a decided increase in the number of red corpuscles.

In conclusion, it may be stated that, possibly, some other origin for Hb. may exist than in the intestine; from all evidences, however, this is the principal source and, in chlorosis, the most important.

DISCUSSION.

DR. CROZER GRIFFITH: The nature and origin of chlorosis, and, indeed, the study of the diseases of the blood in general, has been of particular interest to me for a number of years. It is a strange fact that this disease, of which we see so much, is yet one of whose pathogenesis we know so very little. On that account Dr. Forchheimer's contribution is one of very great value.

Closely allied to the origin of chlorosis is the relation which the disease bears to pernicious anæmia. I may be permitted to refer to it, because it has been claimed within a very few years by speakers before this Association that the two were very closely allied. My own opinion is that which is commonly held, that the two are entirely distinct. Even until very recent times it has been believed that pernicious anæmia was due to some disease of the blood-producing apparatus, especially of the bone marrow. Hunter showed, however, that it was a purely hæmolytic affection, due to the absorption from the intestine of some poisonous substance, oftenest the result of decomposition. In a paper read before this Association by Dr. Burr and myself, two years ago, Hunter's studies upon the liver in pernicious anæmia were reviewed and confirmed. We have also been able to verify the observation made by others, that the red-bone marrow of the long bones, once considered the cause of pernicious anæmia, can be artificially produced by subjecting dogs to frequent and profuse hemorrhage.

Chlorosis, on the other hand, I have always been disposed to consider a cytogenic disorder due to some unknown disturbance of the blood-making apparatus, by virtue of which the red blood-cells were made in sufficient numbers, but there was some defect in the formation of hæmoglobin. We seem almost forced to such a view, because none of the explanations previously advanced satisfactorily account for the production of the disease, at least in all cases. The view of Virchow, that the affection was the result of a congenital smallness of the heart and vessels certainly does not, and the opinion of Bunge, that there was an excess of sulphur in the intestine which neutralized the iron ingested, likewise fails to account for all cases. I will not occupy time by reviewing the other theories which have been advanced.

Dr. Forchheimer's observations throw a new light upon the subject. It

makes the disease analogous to pernicious anæmia in so far that both are, in a sense, of intestinal origin. In no other respect, however, does it associate them. There is one point upon which these experiments particularly bear. Chlorosis must be considered a pure oligochromæmia. In it there is no diminution whatever of the number of red blood-cells, yet the percentage of hæmoglobin is greatly reduced. In the most typical cases of chlorosis which I have seen, those with well-preserved fat but excessive pallor and the symptoms of lack of hæmoglobin, this relation of the blood-cells to the hæmoglobin has been present. Yet a great number of cases of chlorosis exhibit also a reduction, more or less marked, of the number of blood-cells, although it is always much less than the loss of hæmoglobin. This condition has been called chloro-anæmia by Hayem. Strictly speaking, there is no such entity. It is simply chlorosis complicated by anæmia. Now, in the light of Dr. Forchheimer's observations, it can be seen why this must be so. If the trouble in chlorosis lies in the insufficient formation and absorption of hæmoglobin by the corpuscles, due to some affection of the hæmoglobin-formation by changes in the intestine, there is still no reason whatever why the red blood-cells, which are formed entirely independently of any intestinal affection, should not go on being produced just the same. If, finally, there is also a diminution of the number of corpuscles also, it can be readily explained by the nutritional changes in the cytogenic apparatus, such as are liable at last to follow prolonged lack of sufficient oxygenation in any part of the body.

DR. WOOD: Dr. Forchheimer's paper has been one of the most interesting that I have heard read before the Society. In view of the fact that the test relied on for hæmoglobin is a color test, I would like to know whether any control experiments have been made between arterial blood taken from the finger and venous blood taken from the finger, to see if there be not an apparent rise in the hæmoglobin in the simple transversion of capillary into venous blood.

DR. FORCHHEIMER: In regard to the disagreement of Dr. Griffith and myself it is only an apparent one. I believe that the reduction of red blood-corpuscles is well marked in all cases of long-continued chlorosis; and when the degree of reduction of hæmoglobin is sixty and below I believe that chlorosis is first a diminished production of hæmoglobin, and secondarily a diminution in the production of red-blood corpuscles. The thing that I am working at now is to present experimental proof of the view that I have, not by using tolu, but by using the substance that I have isolated. The quantity that can be isolated from three litres of urine is very small, and up to the present time I have not had a sufficient quantity of this substance to make control experiments in the way of producing an artificial chlorosis. I hope to be able to do this in the near future, and at the same time to determine the chemical status of this substance.

I will say, in reply to Dr. Wood, that we have taken all the possible pre-

cautions in the examination of the blood. In peripheral arteries and veins the quantity of Hb. remains the same; in the mesentery it would naturally be different. No single examination of hæmoglobin has been used. We have examined as nearly as we could both arterial and venous blood, and whatever estimations I have given in figures have been verified as far as the hæmoglobin at least ten or fifteen times, and as far as the hæmocytometer is concerned at least four hundred squares have been examined. All of the figures I have given are average results.

NOTE ON USE OF QUININE IN CHOREA.

By H. C. WOOD, M.D.,
OF PHILADELPHIA.

In the *Journal of Nervous and Mental Diseases*, for April, 1893, may be found a paper published by myself upon the character or nature of the choreic movement. The research which is embodied in that paper was undertaken from a purely scientific point of view, without a thought in regard to the treatment of chorea. The results which I reached, however, naturally led to certain therapeutic studies, and in the present paper it is intended to give the results of those studies. When I agreed to read the present paper before this Society I had expected to carry the scientific study of chorea further than it was taken in the article in the *Journal of Nervous and Mental Diseases;* but unfortunately the supply of choreic dogs suddenly failed me, and I have therefore to-day no new experimental evidence to offer. As the paper in the *Journal of Nervous Diseases* may not have been seen by some of my hearers, it may make my present paper more plain if I give a brief *résumé* of the former paper.

Some years since I re-demonstrated what had been previously asserted and denied—that the choreic movement may be, and probably in a large proportion of cases is, of spinal origin. Thinking over the matter, it came to my mind that probably the basis of the choreic movement was failure of the inhibitory function of the spinal cord. Normally, Setschenow's centre and its subordinate apparatus arrest contraction of the muscles concerned in the voluntary movement instantly so soon as the object desired has been obtained; but in accord with my thought, in the choreic child the weakness of Setschenow's centres and its subordinate apparatus is such that it is not able to stop the motor discharge instantly; and so the movement goes on beyond the normal point. I have long taught that quinine is a

stimulant to the inhibitory function of the spinal cord, and that belladonna is a paralyzant to the same. This being the case, it is natural to expect, provided my theory be correct, that quinine, by stimulating inhibition, would check choreic movement, whilst belladonna, by still further weakening inhibition, would increase choreic movement. This *à priori* reasoning I found to accord with the facts. Anyone interested in the details of reasoning and the records of experiments made can find them in the article in the *Journal of Nervous and Mental Diseases.*

If the theory which I have advanced be correct, that in chorea the loss of inhibitory function is the cause of the symptoms, and that quinine is a powerful stimulant to inhibition of the spinal cord, it is a natural suggestion that quinine should be the proper remedy in the treatment of chorea. Nevertheless, failure of quinine to cure chorea would not prove the incorrectness of the theory, for the simple reason that it would be very possible for the remedy temporarily to control, by stimulation, a weakened function and yet have no permanent effect in the restoration of such function. The only test of the value of the drug under such circumstances must be clinical. I have to offer to the Society to-day two series of observations, neither of them as large as I would like.

The first of these series consists of five cases of chorea in dogs treated by quinine, at my suggestion, in the Veterinary Hospital of the University of Pennsylvania. For the report of these cases I am indebted to the House Surgeon, Dr. W. A. Wilfrid Turnbull.

CASE I.—Setter. Chorea of seven months' standing. Quinine. Immediate great improvement. Recovery in a month.

CASE II.—Pointer. Chorea of long standing. Quinine, 24 grains a day at first. No improvement. Increased to 40 grains a day, followed by complete recovery in two weeks.

CASE III.—Violent chorea. Dog could not stand. Quinine, 16 grains a day, followed by immediate improvement; in eleven days dog able to walk; in another week was taken home; a week later entirely well.

CASE IV.—Dog very much emaciated, not able to stand and would not eat. Given immediately 40 grains a day, with whiskey and milk. Choreic movements, which had been violent, in three days had almost disappeared, but the animal was too weak to swallow, and died during the night.

CASE V.—Beagle hound. Marked chorea. Given 48 grains of quinine a day. On the third day vomiting, with marked symptoms of gastritis. Chorea better. Quinine stopped. Gastritis treated for six days. Then 48 grains of quinine a day were given, with great relief of the choreic symptoms, which had returned, but with increased weakness and return of the gastric irritation. Death. Great congestion of the stomach found at post-mortem.

CASE VI.—Spaniel. Very small dog. Violent chorea. Nine grains of quinine a day. Decided gradual improvement, ending in cure.

In considering these cases, it must be remembered that canine chorea is a very intractable disorder. The few cases with which I have had personal experience before this lot, terminated fatally; and Prof. Pearson has told me that during the last year at the University Hospital, previous to the introduction of the quinine treatment, that a number of cases had been treated without one favorable result. There were in the present series, six cases; four cures and two deaths. In each of the fatal cases the choreic movements were controlled by the quinine. My own examination of the cords of choreic dogs has demonstrated to me what I suppose veterinarians generally well know, that in the advanced stages of the disorder the spinal cord undergoes such severe organic alteration that recovery must be hopeless. The record of Case IV. shows that at the time the dog entered the hospital it was in the last stages of emaciation and palsy, dying in three days in spite of careful feeding. In the other fatal case, gastritis, probably caused by the quinine, which was given in very large doses, may have had much to do with the fatal result.

The second series of cases comprises instances of chorea in children.

In the wards of the Pennsylvania University Hospital there have been treated two cases this spring, reported as follows:

CASE I.—M. D., aged seven years. On entrance into the hospital chorea was very violent, so much so that the child could not feed herself at all, and when it was attempted to feed her it was necessary to hold her head in order to put the food in her mouth.

February 3. Commenced treatment.

3*d* to 6*th*. Took 12 grains of quinine a day.

6*th* to 10*th*. Took 15 grains a day.

The improvement at this time was very distinct; the child being able to feed herself. On the tenth day treatment was interrupted by a sharp attack of measles, and by the eighteenth her chorea was nearly as bad as it had been.

18*th* to 23*d*. Took 9 grains of quinine a day.

23*d* to 27*th*. Took 12 grains a day.

27*th* to *March* 28. Took 15 grains of quinine a day.

During this time there were not at any time evidences of cinchonism or other disagreeable effects of quinine. Improvement was steady, and at the time of her discharge, March 28, she was entirely well. No other treatment was used except some cod-liver oil. The child was brought in from the slums, and her original physical condition was very bad.

CASE II.—Jessie ——, aged ten years. Physical condition at the time of

entrance into the hospital very bad. Chorea so violent she could not feed herself at all, and her mother affirmed that she had had it for four years.

February 3 to 6. Took 12 grains of quinine daily.

6*th* to 8*th*. Took 18 grains daily.

8*th* to 12*th*. Took 15 grains daily.

12*th* to 20*th*. Took 24 grains daily.

20*th* to *March* 28. Took 16 grains daily.

No other medicine given except cod-liver oil. The improvement at first was very rapid, the child being able to feed herself in a week; after that it was slower but steady, and at present she simply shows, at times, in one hand, faint traces of choreic movements—most of the time movements are absent. Physical condition very much improved. No evidences of cinchonism or disagreeable effects of the quinine present at any time.

I am indebted to Dr. Chas. S. Potts, Chief of Clinic in the University of Pennsylvania Dispensary, for a report of the nine cases treated there this spring. An outline of the report is as follows:

CASE I.—Female; aged fourteen years. First attack, three weeks' duration; movements very severe; speech much affected and tongue often bitten; neurotic temperament. Ordered 20 grains of quinine daily. Marked improvement in two days; movements entirely ceased and child reported well in five days.

CASE II.—Female; aged fourteen years. Second attack of a few days' duration; movements very severe. Put on the ordinary arsenical treatment, with some relief as regards chorea after some weeks, but with the development of severe gastric inflammation. She was ordered 16 grains of quinine a day; according to statement of mother the movements were markedly lessened by the third day. When she returned to the dispensary twelve days after the institution of the quinine treatment there were no choreic movements.

CASE III.—Female; aged nine years. First attack, three weeks' duration; chorea severe; neurotic temperament. Was treated for three weeks with Fowler's solution, reaching ten drops three times a day. Gastric irritation developing, treatment was continued twenty-five days longer, with five drops of Fowler's solution, three times a day. Chorea now distinctly better, but marked neuritis in both legs. The arsenic was stopped and 9 grains of quinine given daily. In three days the choreic movements had gradually lessened, and the neuritis was better. Two weeks later she showed herself at the dispensary free from neuritis and chorea.

CASE IV.—Female; aged fourteen years. Second attack. First attack lasted three years. Present attack of two months' duration; movements chiefly confined to muscles of face. Given 24 grains of quinine a day. At the end of two weeks the movements were much better; some cinchonism. Case did not report to the dispensary again.

CASE V.—Female; aged eight years. Duration two weeks; movements severe. Given 16 grains of quinine a day; great improvement in three days; complete cessation of chorea in nine days. Medicine stopped, chorea returned in ten days; given quinine, with cod-liver oil, iodide of iron. At the end of two weeks perfectly well.

CASE VI.—Female; aged fourteen years. Second attack. Present one of several months' duration and very violent. Ordered 16 grains of quinine a day; in three days much better. Quinine increased to 20 grains a day. A week later was nearly well. No cinchonism. Five days after no symptoms of chorea.

CASE VII.—Female; aged eight years. First attack, three months' duration; caused by fright; movements severe. Given 16 grains of quinine a day; much better in three days; some cinchonism. No further report.

CASE VIII.—Female; aged eleven years. Second attack. First one lasted four months; was under arsenic and tonics. Symptoms slight; 15 grains of quinine, increased to 20 a day; at first got better; two weeks after institution of treatment was not so well. Put upon the arsenical treatment; at the end of two weeks no better. After this did not report.

CASE IX.—Male; aged twelve years. First attack, one week's duration; very severe. Was given quinine 16 to 24 grains a day, for nine days; no improvement. Was put upon Fowler's solution; in five days better. Two weeks later nearly well.

In looking over the record just given it will be seen that the quinine treatment failed only in two cases, and of these cases one failed to improve upon the arsenical treatment, but the second case was relieved by Fowler's solution. In two cases, Numbers 4 and 7, there was very rapid improvement under quinine, and then no further report. It is practically certain that the children got well and the parents neglected to report the fact. Of the other cases, the average duration under the quinine treatment was about eleven days; no other remedy but the quinine being used. In two of these cases a thorough trial of the arsenical treatment had been made without benefit.

The result of our clinical studies seems to me, therefore, highly favorable to the use of large doses of quinine in the treatment of chorea. A remarkable fact which we especially noticed in those cases which were in the hospital, and therefore could be carefully watched, was the complete absence of apparent physiological action. Thus, a child ten years old, took some 1200 grains of quinine in the course of seven weeks, having part of the time taken day after day twenty-four grains a day. At no time was there any

deafness, tinnitus aurium, disturbance of the stomach or bladder, or other drug symptoms; only a steady growth in the general nutrition.

I have had one or two letters concerning the quinine treatment which seem to me worth noting.

Dr. H. M. Lash, of Indiana, writes concerning

C. F., aged thirteen years, who was brought to the Indianapolis City Dispensary on May 13th, by two attendants; his chorea being so severe that it required two persons to handle him. The disease had followed an acute inflammatory rheumatism. The boy was put on 20 grains of quinine a day; increased to 25 grains on the fourth day. On the third day improvement set in, and on the ninth day the choreic movements had entirely disappeared.

Dr. Frank R. Fry, of St. Louis, writes that in January, 1888, having occasion to give quinine to a patient suffering from severe chorea for the purpose of curing a coincident malaria, he noticed, to his surprise, that the chorea disappeared in ten days; and he states that since that time he has habitually given quinine in chorea, usually with marked improvement.

DISCUSSION.

DR. WHITTAKER: Dr. Wood's paper is very interesting, and the results extremely so. I think the investigations, however, are defective in one regard, and that is in regard to examination of the blood of the choreic dogs. Every one is familiar with the fact that many cases of chorea are toxic, produced by lead, alcohol, and various toxic agents, and that sometimes it is a manifestation of malaria. It would be very interesting to know if malaria in the dog manifested itself as chorea.

DR. WELCH: I can answer Dr. Whittaker's question because Dr. Berkley and I have made a careful study of the pathological anatomy of chorea in the dog, and examined the blood in one case. We found a protozoic organism in the intestine, but coverslip preparations did not show the presence of the malarial or other organism in the blood.

DR. OSLER: Canine and human chorea are not identical diseases. They present two very remarkable differences. In the first place the movements in a choreic dog are entirely different from those seen in the choreic child; though they are identical with the movements in hysterical chorea, that is to say, so far as I have ever seen, they are rhythmical.

DR. WOOD: Not always.

DR. OSLER: The other important difference is in the pathological anatomy. So far as my own observation goes, the chorea in the dog is never

associated with endocarditis, whereas, fatal cases of chorea in children are, as a rule, associated with endocarditis.

With reference to the treatment of chorea with quinine, Dr. Wood's results do not appear to be in any way extraordinary. To treat a disease like chorea with a drug which does good only within ten days or two weeks is not very satisfactory and not much better than arsenic and other remedies. We have used it in several cases. In one very interesting case, that of a deaf and dumb child, with movements so violent that she had to be carried into the hospital, and was unable to feed herself, the drug did not modify the disease at all, given in doses of 5, 6, and 8 grains three times a day.

DR. WOOD: I did not mean at all in this paper to enter into a general discussion of chorea, for the simple reason that I did not feel justified in occupying the time of this assembly, but as the matter has been brought up, perhaps I may be pardoned if I take a few minutes in discussing it. I do not believe, myself, that chorea is a disease at all; it is a condition of the nervous system which may originate from many causes. It is a certain condition of the great nerve centres which may be produced by the rheumatic poison and possibly by the malarial poison, and it may be produced by lead, by arsenic, and by various conditions. My thought is at present that the underlying factor of this condition of the nervous system is a weakening, not only or not chiefly of the motor power, but a weakening largely of the function of inhibition. There is an absolute lack of clearness of thinking on the part of many of the profession on account of the simple fact that the word chorea is used with so many different meanings. Cases which are called chorea have often no more definite pathological relation with one another than if they were called by different names. Take the so-called local chorea and the rhythmical chorea, which Dr. Osler has spoken of, and the chorea of the child; they may be essentially different conditions. But there is a group of cases which we every day see in the spring in our nervous dispensaries, of children with impaired nutrition and often with the rheumatic diathesis, which is clinically a group which we can distinctly recognize. It is absurd, to my mind, to make the objection that this clinical group may be malarious. It cannot be malarious. We know the history of rheumatism and we know the history of the great mass of these cases; they have nothing to do with malaria.

In regard to the chorea of the dog and of the child, I do not mean to say that they are the same thing, though they certainly have a great many symptomatic relations, and they certainly are constitutional conditions and have similar anatomical conditions underlying them. Endocarditis may exist without chorea, and chorea without endocarditis, and the union of the two is because they have a root in the common cause and not because they are essentially one a part of the other; they have a connection at the bottom, but one does not outbud from the other; when they coexist it is an accident. The chorea of the dog grows out of a constitutional affection precisely as that of the child grows out of a constitutional condition.

EYE TUBERCULOSIS AND ANTI-TUBERCULAR INOCULATION IN THE RABBIT.

By E. L. TRUDEAU, M.D.,
OF SARANAC LAKE, NEW YORK.

At the last meeting of this Association I presented a paper on the "Treatment of Experimental Tuberculosis," illustrating the influence of such treatment on eye tuberculosis in the rabbit by photographs and living animals. The two last conclusions reached were as follows: "Experimental tuberculosis in the rabbit's eye can be cured by such injections. The permanency of this cure has not yet been established." A more extended experience has shown me that the cure of inoculation tuberculosis in the rabbit's eye, by this method, is by no means always a constant result, or one which can be brought about invariably at will. I have failed often where I had every reason to expect success, and I have succeeded where I had no special reason to hope for a favorable result.

This inconstancy in results may be explained by the great difficulty of controlling the relation existing between all the factors involved in the problem, such as the virulence of the bacilli injected, their number, the virulence of the microbes from which the tuberculin was made, and the degree of individual resistance possessed by each animal. Cures do occur, however, and appear to have a certain degree of permanence, as the two animals I now show you illustrate. These rabbits were inoculated in the eye with cultures of tubercle bacilli of human origin more than a year ago. The eye of the untreated control is cheesy and atrophied; that of the treated animal shows but the fibrous evidence of the inflammatory changes of which it has been the seat; the sight is unimpaired, the cornea clear, the inoculation wound a mere corneal scar, the iris dilated and showing on its surface small, grayish, fibrous specks at the site of the once

evident miliary tubercles, is still adherent to the lens by fibrous bands, while the vascularity of the eye is normal. The present appearance has remained unchanged for six months.

Hitherto the tubercle bacillus has always been considered as a pathogenic microbe, having but one source and possessed of a very constant degree of virulence. More recent researches by Muffici, Koch, Metchnikoff, Courmont and Dor, and Loeb have taught us that the virulence of this germ varies greatly and that there are two distinct races of tubercle bacilli, the mammalian and the avian. Loeb's experiments, made in Koch's laboratory, showed that bacilli cultivated uninterruptedly for nine years, and having descended from the original cultures used by Koch in his first experiment, which then killed both guinea-pigs and rabbits within six to ten weeks, were no longer pathogenic for rabbits and but slightly so for guinea-pigs. Principally through the labors of the above-mentioned investigators, it has also become known that the avian tubercle bacillus is apparently a race by itself, and that it presents certain quite constant cultural and pathogenic peculiarities not observed in the microbe originally discovered, studied, and described by Koch. Whether these variations have merely been acquired by Koch's bacillus as the result of a long parasitic life-history in the organism of birds, or whether they indicate a permanent difference of race, is still a disputed point. As yet, however, it has been found impossible by laboratory and inoculation experiments to show that either variety of these germs can be transformed into the other.

In 1890 I presented and described before this Association cultures of the tubercle bacillus which were not pathogenic for guinea-pigs and which showed marked cultural variations from the standard. The original source of these bacillary growths was somewhat doubtful, and I supposed them to have become attenuated while under cultivation. In the light of recently acquired facts, however, it is quite evident that these attenuated cultures were bird tuberculosis, and the description then given will answer very well for the avian microbe, as we now know it.

In growing this variety of the tubercle bacillus from the lesions of the tubercular birds, not only have I been able to confirm many of the observations made by Muffici, Koch, and the French experi-

menters, but I have been struck as well with two marked peculiarities which I have not seen described.

1. The ease with which the chicken bacillus adapts itself to a saprophytic existence, which is in strong contrast to the well-known difficulty of obtaining first growths of Koch's bacillus in artificial media, for the avian microbe grows readily direct from the lesions of birds in most of the media in use, whether solid or fluid.

2. The strong anærobic attribute possessed by the bird bacillus which enables it to thrive readily within and beneath fluid media as well as on the surface, while the human microbe only grows when floated on the surface of liquids and in constant contact with oxygen, but develops almost imperceptibly or not at all when immersed. The human bacillus has been found by all observers to be almost harmless for birds, though, in rare instances, intra-peritoneal inoculations may cause an eruption of tubercle in these animals. Intra-peritoneal re-inoculations of this tubercle, however, prove negative, and the animal remains healthy.

The avian bacillus, when fresh from the lesions of the birds or when cultivated but for a short time in artificial media, is almost harmless for dogs and guinea-pigs. Rabbits are, however, more susceptible to it, and die readily from intra-venous, intra-peritoneal, and intra-thoracic injections of not excessive amounts of these cultures. On autopsy they may show either extensive generalized tubercular lesions or they may present no evidence of tubercle in any organ, but are extremely emaciated only, as if they had died of chronic septic intoxication. When a small amount (0.05 to 0.25 of liquid culture, grown a month, direct from the chicken) is injected under the skin the animal generally recovers, an abscess is formed at the site of the inoculation; this tends slowly to soften and become diffuse, and, finally, if the animal survives, disappears entirely. This brings us to the subject of preventive inoculation.

Anti-tubercular inoculation was first tried by Falk in 1883, and all attempts in this direction have resulted, until recently, in but an unbroken record of failures. In 1890 I added my name to the list of those who found it impossible to produce immunity in animals by this method.

In 1890 Martin and Grancher and Courmont and Dor claimed to have produced in rabbits a certain degree of immunity by previous

inoculation, after Pasteur's hydrophobia method, of avian tubercle bacilli of graded and increasing virulence.

These vaccinations were, however, frequently fatal to the animals, and the immunity obtained was but relative. Richet and Hericourt have since claimed to produce complete immunity in dogs by intravenous inoculations of bird tubercle bacilli. These experimenters found that, though harmless to the dog when first derived from the chicken, bird bacilli, by long cultivation in liquid media, became pathogenic for the animal, and, by thus grading the virulence of the injections, complete immunity against any form of tubercular infection is produced in the dog. As yet these striking results have not been confirmed.

The animals which I now present to you illustrate an attempt which I have made along the same line to produce immunity in the rabbit. Cultures grown directly from the chicken's lesion in bouillon, first, five weeks, then six months, were twice injected subcutaneously at intervals of twenty-one days, in doses of 0.05 and 0.25, and a third injection of a still older culture was occasionally given. About one in four of the rabbits died within three months, profoundly emaciated, but without any visible tubercular lesions. The remaining animals recovered and were apparently in good health, when, with an equal number of controls, they were inoculated in the anterior chamber of the eye with cultures of Koch's bacillus, derived from the tuberculous lesions of the rabbit and cultivated about three months on glycerin-agar. The results of these inoculations present many points of interest.

In the controls, as is usually the case, if the operation has been done carefully and aseptically, and if the amount injected has been small and well diluted, two days after the introduction of the virulent material into the eye, little or no irritation is observed, and little is to be noticed for two weeks, when a steadily increasing vascularity manifests itself, small tubercles appear on the iris, which gradually coalesce and become cheesy. Intense iritis and general inflammation of the structures of the eye develop, the inoculation wound becomes cheesy, and in six to eight weeks the eye is more or less completely destroyed and the inflammation begins to subside. The disease, however, remains generally localized in the eye for many

months, and even permanently, according to virulence and number of microbes injected.

In the vaccinated animals, on the contrary, the introduction of the mammalian bacilli at once gives rise to a marked degree of irritation. From the second to the fifth day the vessels of the conjunctiva are tortuous and enlarged, whitish specks of fibrinous-looking exudation appear on the iris and in the anterior chamber, and more or less intense iritis supervenes; but at the end of the second to the third week, when the eyes of the controls begin to show progressive and steadily increasing evidence of inflammatory reaction, the irritation in those of the vaccinated animals begins slowly to subside and the eyes to mend. The vascularity is less, the whitish spots of fibrinous material appear smaller, the structures of the eye become clearer, the inoculation wound is but a bluish, fibrous scar, until, in from six to twelve weeks, in successful cases, all irritation has disappeared and the eyes present, as in the animals I now show you, but the fibrous evidence of the traumatism and the inflammatory processes which have been set up by the inoculation.

In all the controls, as you see, the inoculation wound is cheesy and the cornea and iris are more or less destroyed by tubercle and cheesy areas.

Some of the protected animals slowly relapse, and the one I now show you has small tubercles growing on the iris; but, even in such eyes, the entire absence of caseation in the eye is noticeable, and the disease progresses almost imperceptibly. I have repeated these experiments on three sets of rabbits with almost the same results each time. The vaccinations, as practised, are of themselves in some instances fatal; but the fact remains that where a recovery takes place a marked degree of immunity has been acquired.

I do not lay any claim, therefore, to have produced a complete or permanent immunity by a safe method; but it seems to me that these eyes constitute a fair demonstration of the fact that, in rabbits, preventive inoculations of bird bacilli can abort an otherwise progressive localized tubercular process so completely as to prevent destruction of the tissues threatened, and that the future study of anti-tubercular inoculation may not be quite as hopeless as it has, until recently, appeared.

DISCUSSION.

DR. WELCH: I will take this opportunity to report the results in three rabbits which were exhibited before this Association at the last meeting in May, 1892. Each of these rabbits had been inoculated by Dr. Trudeau, about two months previously, with pure culture of the tubercle bacillus into the anterior chamber of the right eye and into the right thoracic cavity. One of these rabbits had been reserved as a control; a second had been treated, after the inoculation, with injections of bacterio-protein solution; and the third with injections of the filtrate of liquid cultures of the tubercle bacillus in the manner described by Dr. Trudeau in his paper read at the last meeting, and printed in Vol. VII. of the *Transactions*. It will be remembered that the control rabbit showed marked tuberculous disease of the inoculated eye; the rabbit treated with bacterio-protein showed conical protrusion and opacity of the cornea, which was vascularized, and also the marks of old subcutaneous abscesses at the points of injection; and the rabbit treated with the filtrate showed clear cornea and media with a small, opaque, grayish-white mass in the anterior chamber and adherent to the iris. Dr. Trudeau requested me to take charge of these rabbits after the meeting, and to continue the treatment which he had begun. This treatment was carried out in accordance with the directions.

The rabbit which was treated with bacterio-protein solution died June 14, 1892. For several days previous to its death it was weak and unable to stand. It died very much emaciated and apparently from exhaustion. An abscess developed near the right lower jaw. The following is extracted from the notes of the autopsy: The right cornea protrudes in a conical form, is opaque, and vascularized over most of its extent, and superficially ulcerated at the most prominent point. The iris is apparently represented by a thin, opaque, membranous mass adherent to the posterior surface of the cornea. The lens is dislocated into the anterior chamber. In the membranous tissue representing the iris are four or five firm, opaque, yellowish-white tubercles about the size of a pin's head. The aqueous and vitreous media are turbid but not purulent. The left eye is normal.

There are old adhesions between visceral and parietal pleuræ of right side over a small patch where there is a small, firm, opaque, whitish mass.

The scars and scabs of old abscesses and ulcers can be seen on the skin of the back at points corresponding to the injections of the bacterio-protein solution.

The abscess near the jaw contains short and long bacilli readily staining with aqueous solution of methylene blue.

There are no tubercles except the old ones in the right eye and right pleura.

The rabbit which had been treated with the filtrate of tubercle culture died October 28, 1892, in consequence of acariasis of the ears (psoroptes cuniculi) which at the time proved fatal to several of the rabbits in our stalls.

The cornea and media of the right eye were perfectly clear and normal. In the upper segment of the anterior chamber adherent to the iris was a small whitish speck, not exceeding one-half millimeter in diameter, adherent to the iris. No tubercles could be seen in the iris or in any other part of the body. The only lesions found were the customary ones of acariasis of the ears.

The control rabbit died December 19, 1892. It had been noticed to be sick and weak for several days before death. The following is from the record of the autopsy:

"The right cornea is opaque and bulging. About its centre is an ulcerated opening through which dry, opaque, cheesy material protrudes. The anterior chamber and the iris are filled with the same caseous material. The lens cannot be found. The posterior half of the eyeball is atrophied. A gland in the orbit contains several small, opaque, yellowish-white tubercles, the largest the size of a pin's head.

"Over the right side of thorax is an encapsulated abscess with caseous contents 4½ cm. in length and 3½ cm. in width, lying over the pectoral and intercostal muscles. Attached to both visceral and parietal pleura of right side are eight encapsulated, pedunculated or loosely sessile, caseous masses, varying in size from a pin's head to a bean. There are no tuberculous nodules elsewhere than in the situations mentioned. The animal is emaciated and presents increased quantity of serum in the serous cavities. No bacteria can be detected in cover-slip preparations from the caseous masses."

It will be observed that none of the rabbits, not even the control, developed generalized tuberculosis. Localized tuberculosis is not uncommonly the sole result of inoculation of rabbits with tuberculous material.

The control rabbit, however, suffered destruction of the right eye from caseous panophthalmitis, and developed multiple caseous foci near the seat of inoculation in the right thorax.

The rabbit treated with bacterio-protein developed less extensive tuberculosis at the points of inoculation than did the control rabbit, but still it presented several small, discrete, tuberculous nodules at these points, and the cornea became bulging, opaque, and vascularized.

The rabbit treated with the filtrate showed no visible tubercles whatever in either of the two seats of inoculation or elsewhere, and died seven months after inoculation from an accidental affection, acariasis auriculorum.

The results in this series of experiments are therefore confirmatory of those already reported by Dr. Trudeau.

DR. WHITTAKER: I am glad the subject has been brought up for discussion here, because the impression seems to have gone out that the opinion of this Society is adverse to the use of tuberculin, from some reports that were made at a previous session of the Society whose tenor seemed to be that the remedy was not only useless but for the most part actually injurious. We have since that time gotten new light on the nature of the tuberculous process, which

shows how laboratory tuberculosis differs from the human tuberculosis. But some of us have continued the use of tuberculin regularly, and I have myself administered it daily since that time, both in private and hospital practice, and I have never seen any reason for a modification of Koch's first opinion, as he expressed it, in regard to cases of pure tuberculosis. What I have observed in my practice has been this: that there has been a singular and early relief from the depressing action of the disease, first of all, and more so than from any other method of treatment. We assume that the tubercle bacillus produces a toxine and that this toxine causes this condition of depression. Although a minority of the cases show an exaltation, a *spes phthisica*, yet in most cases there is a marked tendency to melancholy. In the course of a week or two, or after five or six injections of tuberculin, patients experience relief from this condition, and they continue to show this relief until some complication occurs. Tuberculosis is a complicated process. It runs a continuous course for a time, and then there is an aggravation, and the individual has what we call a relapse. That relapse we believe now to be due to a secondary invasion.

Cornet called attention to the fact that tubercle bacilli grow slowly and do not produce those conditions which the invasion of streptococci and other pyogenic organisms are known to do. There are cases attended with a large amount of consolidation in the vicinity of the cavity in the lung-tissue, and some of these organisms are believed to be connected with this consolidation process. When that occurs, of course the gain which has been accomplished is lost. Then after two weeks or so the patients gradually improve, and then relapse again. This is the general history of these cases: that they become complicated with some other affection. Individuals who are being treated with tuberculin also show these relapses for a time, but in some cases will recover entirely from the disease. Where we have mixed infections, of course the tuberculin does little or no good, and for the most part it does harm. It is the reckless administration of tuberculin in these cases of so-called hectic fever that has brought tuberculin into disrepute.

The best evidence we have goes to show that tuberculin produces a distinct hyperæmia of the lung. The tubercle bacillus itself produces a hyperæmia, but it is a limited hyperæmia. The tubercle bacillus would die out in many cases did it not make wounds and cause wound infections. For the most part these complicctions are due to secondary infections, the so-called wound infections. These cases are not benefited by tuberculin, because it increases the hyperæmia and leads to increase in the consolidation process. At least that is the testimony of the best pathologists. I may quote Ribbert in this regard.

There is in my mind, therefore, in case of pure tuberculosis, no doubt about the action of tuberculin—it is the only specific remedy. All other remedies act only through the avenues of nutrition and resistance to invasion: such remedies as cod-liver oil, etc. Climate will act upon streptococcus infection as nothing else will. I have seen cases go out to Colorado Springs and get well and stay well as long as they remained there. But many of these patients

have to remain there. The cases that recover after the use of tuberculin do not have relapses. The patients that recover from cod-liver oil, or arsenic, or whatever is used, only partially recover. The fire is put out, but coals are left. The patients who only have tuberculosis in its inception, having, perhaps, a light bronchial catarrh at the apices, or are still in the pre-physical state of tuberculosis where we only make the diagnosis by the discovery of the bacillus, these individuals when they are rescued by tuberculin are rescued completely for the most part. I refer also to cases in which we make the diagnosis of doubtful cases of fever or debility by tuberculin. An individual falling into declining health, without any lung symptoms, who has been treated by tonics, change of scene and climate, etc., without success, when treated by tuberculin may be found, by the reactions to this treatment, to be the victim of tuberculosis. When such cases are treated with tuberculin we rescue them completely in the majority of cases.

It does not take so long a time to effect a cure as is commonly asserted. Most of these cases are rescued in two or three months under careful use of the remedy, and these cases, I repeat, do not fall back into the condition of patients who return home from Colorado improved, but to fall victims anew to the disease. Patients who have been brought up from one-half a milligram to ten centigrams do not relapse. I have not seen a single relapse; but, of course, I speak only for a year as the longest time under observation as yet.

In connection with the rabbits seen here to-day, which are, by the way, historic rabbits, we all remember what an excitement went over the land when it was announced that tuberculosis could be communicated by inoculation, and then what disappointment was felt when that fact seemed to be overthrown by subsequent investigation of Sanderson, Fox, and more particularly by Cohnheim, who found that tuberculosis could be conveyed by innocent matter, elder pith, etc.

Then, finally, when these men repeated their experiments on the eyes of rabbits, they found they had made a mistake before. It is rather a curious fact that the confirmation of the existence of the specificness of tuberculosis came to us through the eyes of rabbits, and it seems now that the confirmation of the value of tuberculin is to be made in the same way.

SOME PROBLEMS IN THE ETIOLOGY AND PATHOLOGY OF TEXAS CATTLE FEVER, AND THEIR BEARING ON THE COMPARATIVE STUDY OF PROTOZOAN DISEASES.

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In a monograph on this interesting malarial disease of cattle, recently published by the Bureau of Animal Industry of the U. S. Department of Agriculture,[1] certain conclusions were reached which I will briefly quote in order to make familiar the facts upon which this communication is based :[2]

1. Texas cattle fever is a disease of the blood, characterized by a destruction of red corpuscles. The symptoms are partly due to the anæmia produced; partly to the large amount of débris in the blood, which is excreted with difficulty, and which causes derangement of the organs occupied with its removal.

2. The destruction of the red corpuscles is due to a micro-parasite which lives within them.

3. Cattle from the permanently infected territory of this country, though otherwise healthy, carry this micro-parasite in their blood.

4. Texas fever may be produced in susceptible cattle by the inoculation of fresh blood containing the micro-parasite.

5. Sheep, rabbits, guinea-pigs, and pigeons are insusceptible to inoculation.

6. Texas fever, in nature, is transmitted from cattle which come

[1] Investigations into the Nature, Causation, and Prevention of Texas or Southern Cattle Fever. By Theobald Smith and F. L. Kilborne, 1893. For a more condensed account of this disease see *Centralblatt f. Bakteriologie*, xiii. (1893), p. 511.

[2] Loc. cit., p. 151.

from the permanently infected territory to cattle outside of this territory by the cattle tick (*Boöphilus bovis*).

7. The infection is carried by the progeny of the ticks which matured on infected cattle, and is introduced by them directly into the blood.

Included in these general propositions there are a host of minor problems of which many have been lightly touched upon and only a few seriously considered in the monograph referred to. Some of these are of considerable general interest, and to these I wish to call your attention briefly.

Texas fever, as it is usually met with, is characterized by high fever, rapidly progressive anæmia, and, in almost all fatal cases, hæmoglobinuria. During the fever there are present in the circulating blood (from the skin) a small percentage of red corpuscles invaded by a peculiar protozoan parasite. It consists of two pear-shaped bodies with their tapering ends lying close together. In stained preparations a very delicate connecting line is frequently traceable. The largest micro-parasites contain in the enlarged end of each pyriform body a very minute, dark globule, and more rarely a vacuole-like structure. These large forms stretch nearly across the corpuscle. Each body may measure 4 μ in length. The rounded end then measures 2.5 μ across. A corpuscle may be invaded by two and even three parasites.

Amœboid changes are easily observed even at the temperature of the room. It seems that the largest pyriform bodies are rigid and that only the smaller intermediate forms make use of this property of motion. From the observed fact that pyriform parasites are nearly always found in the organs when the animals are killed and dried films quickly prepared, I infer that the micro-parasite makes use of its mobility only under adverse circumstances, and that the pear-shaped outline is the ordinary quiescent form.

If the animal survives the acute fever, it may die just after the subsidence of the high temperature, which rarely lasts longer than a week or ten days. An engorged spleen and a liver disintegrated by necrotic and fatty changes are the most marked lesions found at this stage. If the animal survives it begins life anew with about 1.5 million red corpuscles per c.mm.

This, however, is not the end of the disease. After an intermis-

sion of several weeks, during which, in rare cases, there may appear one or more attacks precisely like the one described, except in severity, there is ushered in a peculiar mild type of the disease, to which I wish to call your attention more closely. There is, in most cases, nothing in the outward appearance of the animal to warn us of the presence of this mild disease except a high evening temperature. When the blood is examined during the climax of this secondary attack some very striking appearances are presented. In carefully dried and heated films of blood stained in alkaline methylene blue we observe a large number of enlarged corpuscles or macrocytes, and if the anæmia is very advanced these may become still larger and retain a feeble bluish stain or be filled with minute stained particles or granules. These changes, which I had the honor to discuss before this Association in 1891,[1] indicate a very active introduction of new, partly immature, corpuscles into the circulation as the immediate result of a progressive destruction of corpuscles.

The important objects in the field, however, are the infected corpuscles. These are in the beginning of the attack of normal size and appearance. The newer, enlarged corpuscles are attacked later on when the normal forms have disappeared. In unstained, undiluted fresh blood, when the corpuscles are spread out in a uniform layer and slightly flattened out by the weight of the cover-glass, and then only, the parasite may be seen as a round spot about 0.5 μ in diameter, free from hæmoglobin, situated within the corpuscle on its very border. In dried and heated films of blood, the contained parasite stains deeply in alkaline methylene blue, and appears as a minute coccus-like body on the periphery of the corpuscle. Occasionally two parasites are seen in the same cell. In many cases a partial division of the body is evident. The larger pyriform bodies of the acute fever are absent from the circulating blood in this secondary attack, and are only rarely detected in the convalescent stage after the minute parasite has vanished and the number of corpuscles is rising.

The infection of the corpuscles in the mild fever lasts usually a month, sometimes the period is longer, sometimes shorter. Although the infection to the eye may appear to be growing and the percentage of infected corpuscles actually rising as the fever progresses, this is

[1] Transactions, vol. vi.

not altogether true, for if the estimated percentage of the red corpuscles actually in the circulation be calculated, the number of infected cells is found to be pretty constant except at the beginning and at the end of the attack. In other words, the vascular system appears to be flooded by about the same number of parasites for several weeks. This number is approximately half a million per c.mm. There may be one or more oscillations in the course of the disease, *i. e.*, the infected corpuscles may become very few in number, and then reappear again in abundance. The rate of destruction is about one-fourth that of the acute fever.

That the coccus-like intra-globular body of the mild fever is a parasite, and not an accompanying or resultant condition of the anæmia, has been fully discussed in the monograph referred to, and I may, therefore, pass it over here. The identity of the coccus-like and the larger pyriform parasite as two stages of the same organism has also been discussed at length, and I refer in this place only to the strongest argument in its favor, the regular appearance of the relapse in those animals in which the disease has been produced by a single inoculation of infected blood, and which have survived the first acute attack.

This mild type of the disease I first observed among a considerable number of animals infected in the fall of the year. At that time I interpreted it as a mild autumnal variation of the acute fever. In succeeding years it was frequently observed, and mostly by accident, in animals which had passed through the usual acute fever and which had been on the way to recovery for several weeks. Their presence on infected fields made me regard such secondary attacks as the result of reinfection by young cattle ticks of a succeeding generation. This mild form was further more observed in most calves and in a few adults prematurely infected on pastures in early summer. In these latter cases the disease passed into a more or less acute fever, and both small and large forms of the parasite were detected in the blood before death. Finally, the regular appearance of the mild form after the acute fever in animals inoculated but once furnished the basis for a more accurate interpretation of the mild disease as a true relapse in most cases. There is reason to believe, however, that very rarely it may appear independently of a recognizable acute attack. An examination of the history of the individual cases in the mono-

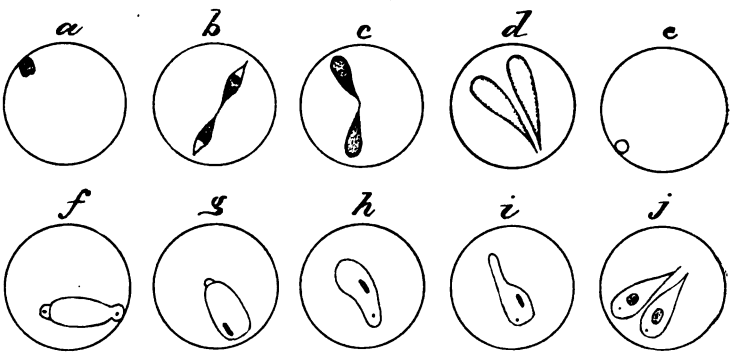
graph referred to will reveal much variation in the intensity and duration of the acute and the succeeding mild type. There may be several acute attacks, accompanied each time by the appearance of large parasites in the blood, and followed by a slight final attack in which only the coccus-like stage of the parasite is detected. Or there may be a short acute fever accompanied by a correspondingly slight reduction in the number of red corpuscles, followed one or two weeks later by a prolonged relapse, in which the number of red corpuscles may finally reach a lower level than in a severe acute attack.

Having thus very briefly sketched the salient characters of this disease, I am now prepared to complete the cursory description of the still partly hypothetical life-history of the micro-parasite before attempting any interpretation of the observed phenomena. The earliest stage we must regard as one free in the blood. This I have assumed to be an exceedingly minute motile swarm-spore which penetrates the corpuscle and comes to rest on its very edge as the coccus-like body already described. Here a partial division takes place which gives rise to the twin pyriform body. All stages between the coccus-like and the large pyriform bodies have been encountered in different animals in the organs. Slight variations in the size of the parasite in different corpuscles of the same preparation are not uncommon. The two members of the twin parasite are always of the same size. The younger forms take basic dyes very readily. The largest are stained only on the periphery. The unstained central portion frequently presents a peculiar spore-like lustre. The conception of a swarm-spore as the youngest stage was due to a discovery made in 1890 of the presence of exceedingly minute bright bodies within the red corpuscles in health as well as in Texas fever. These bodies are frequently in motion, and some change their place in the corpuscle very rapidly. To these bodies I shall revert later.

The multiplication of the micro-parasite in the blood is still an unsolved problem. At first I was inclined to look upon the intra-globular stage as perhaps only a fragment of the life-history of an organism which might complete its existence in some organ and thence send forth into the blood the youngest stage. In hunting for such a hypothetical life-history I encountered a peculiar sporozoon in the intestinal villi, which, however, was soon found to be not uncommon in healthy cattle. The *Sarcosporidiæ* next claimed

attention, especially those forms so abundant under the endocardium. Here likewise a difference between diseased and healthy cattle could not be demonstrated. The theory that this organism is, after all, only a simple blood parasite seems to harmonize best with observed facts. This is supported by the prolonged existence of the parasite in the blood of insusceptible animals. The inoculability of the disease and its exclusive dissemination by blood-sucking ecto-parasites likewise favor the simpler interpretation. In regard to the reproductive phase, it may not be very wide of the truth to look upon the minute dark globule present only in the largest parasites and always situated in the central part of the enlarged end as a spore form. Since the parasite becomes double in every corpuscle the multiplication would be represented by a geometrical progression with a common ratio of two.

FIG. 1.



Semi-diagrammatic illustrations of some of the observed forms of the Texas fever parasite.

(*a* to *d* inclusive, from dried and stained films—alkaline methylene blue.)

a. The peripheral coccus-like stage seen only in the circulating blood of the mild fever or relapse. The parasite in this case is shown in a state of division.

b. Spindle-shaped forms from the capillary blood of the myocardium in the acute fever. The peripheral end of the twin parasite is only very feebly stained.

c. Pear-shaped forms, more uniformly stained, from the myocardium.

d. Large pyriform bodies with only the periphery stained as they appear in the circulating blood of the acute stage and in the convalescent stage after both the mild and acute attack.

(*e* to *j* inclusive, from fresh, undiluted, unstained blood.)

e. The early coccus-like stage of the parasite in the mild fever appearing as a minute vacuole on the border of the corpuscle. (To be compared with *a*.)

f. An amœboid form of the acute attack. Three hours after the withdrawal of the blood (70° F.).

g. The same body one hour later.

h. An amœboid form from an acute case three hours after the withdrawal of the blood (75° F.).

i. The same form a minute later.

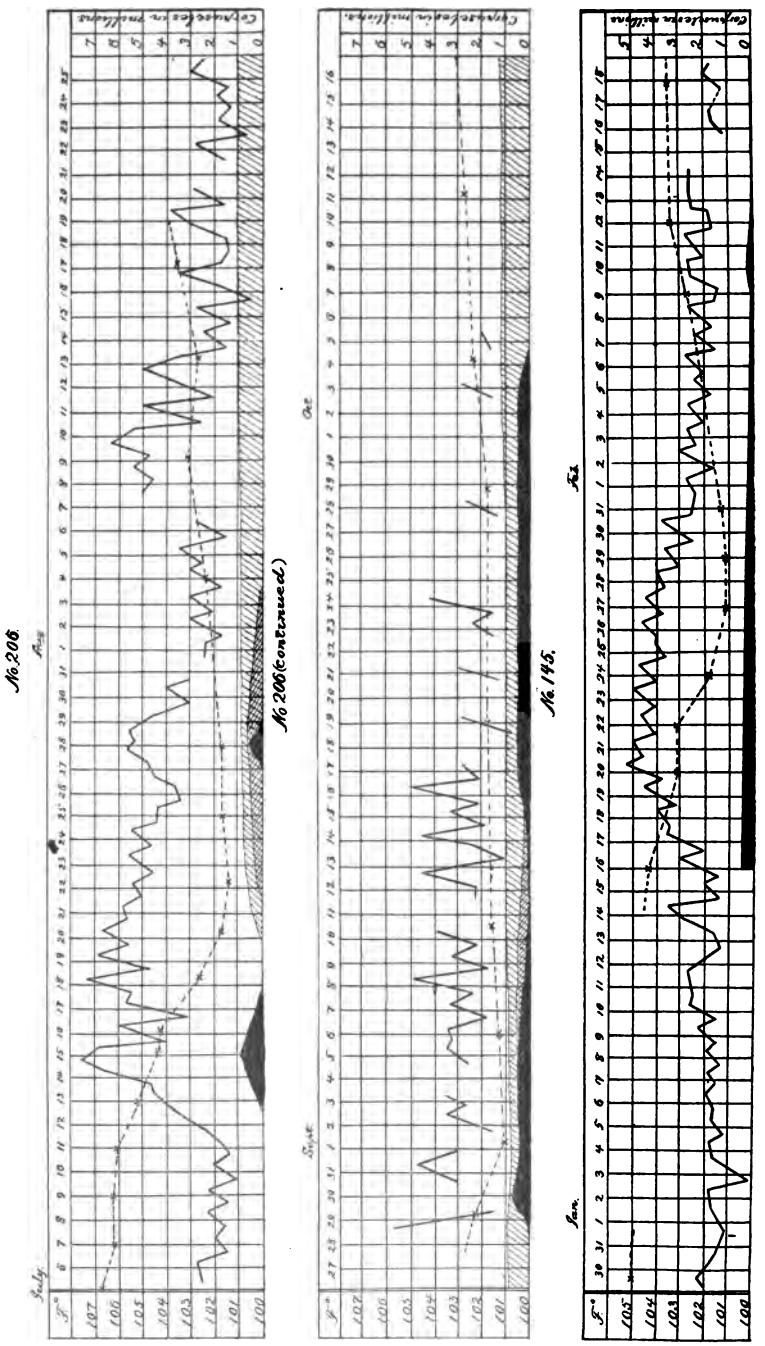
j. Pyriform bodies with minute globules and vacuoles (?) from the blood during convalescence. (To be compared with *d*.)

In attempting to interpret the differences between the acute fever, with its high temperature, its rapid destruction of red corpuscles, its poverty of infected corpuscles in the circulating blood, and the mild fever or relapse, with its slower course, lower fever, numerous infected corpuscles containing only the young stage of the parasite, I am led to consider the latter as a phenomenon of partial immunity brought about by the acute fever, in virtue of which the intra-globular development of the micro-parasite is retarded. Other agencies besides a foregoing acute attack, which favor the host at the expense of the micro-parasite, such as a slight initial infection, youth, season of the year, etc., may, perhaps, bring about the same result. The plausibility of this theory is shown by certain easily demonstrated facts. Thus the small number of infected corpuscles detected during life in the acute fever, in spite of the enormous destruction of such cells going on (from one-half to one million in a c.mm. per day) is explained by the rapid death of the infected corpuscles and their lodgment in large numbers in the capillary system as foreign bodies. This is easily verified by killing an animal in the height of the fever and examining stained cover-glass preparations of the various organs. I take the liberty of quoting such a case by way of illustration :

No. 163 had a temperature of 106.8° F., August 24th. Red corpuscles 3,388,800. On the following day the temperature was 107°, red corpuscles 2,645,000. Killed on the same day : the blood from the skin, from both ventricles of the heart, from the skeletal muscles, and the red marrow, contains only a small number of corpuscles (1 to 2 per cent.) with large parasites. On the other hand, the spleen contains about 5 per cent., the liver and kidney from 10 to 20 per cent., the heart muscle nearly 50 per cent. of infected corpuscles.

In this connection I may cite a fact which has frequently puzzled me. In the acute fever some of the infected corpuscles, especially those which have a decidedly wrecked appearance, have delicate threads radiating from the periphery and more rarely from the disk. These threads are about as coarse as fibrin and as long as the diameter of the corpuscle. The appearance presented by the wrecked, dark corpuscle, with its contained pale parasite and radiating fibrils, some in slight motion, might lead one to believe that this protozoon was provided with flagella which pierced the enveloping membrane

FIG. 2.


No. 206
No. 206 (continued.)
No. 195.
July.
Aug.
Sept.
Oct.
Jan.
Feb.
Temperature in Fahrenheit degrees.
Temperature in centigrade degrees.

The charts on the opposite page are a graphic representation of the temperature, the destruction of red corpuscles, the parasites in the circulating blood, and the changes in the corpuscles due to the anæmia.

No. 206. Case produced by the intravenous injection of blood from a healthy animal from the enzootic territory.

The heavy continuous line represents the temperature, the dotted line the number of red corpuscles. The crosses on this line indicate the dates of the blood examinations.

The black areas indicate the absolute number of infected corpuscles in the circulation. The area shaded by the single set of oblique lines represents the number of macrocytes, but only approximately. The areas shaded by a double set of oblique lines represent the number of macrocytes which retain a feeble stain or contain stained granules.

The black areas on the upper chart represent infection of the blood with large intra-globular parasites (acute attack), the black areas on the second chart, infection with the small intra-globular stage (relapse). Unfortunately the temperature record during the relapse is incomplete. From the charts it will be seen that there is an acute attack characterized by several exacerbations and followed by a prolonged mild attack or relapse.

No. 145. Explanation of lines, etc., as above. The mild attack was detected after a long interval during which the blood was not examined. Hence the abrupt beginning of the black area. The temperature, however, indicates that the attack had just begun. The black area represents the infection of corpuscles with the small coccus-like stage of the parasite.

For a complete history of these cases see the monograph referred to, pp. 227, 256.

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of the invaded corpuscle. The probable explanation is that these corpuscles have broken away from some capillary plug where they had been bound to others by threads of fibrin. This view is supported furthermore by the occurrence of the occasional agglutination of infected corpuscles to others into groups of five or six.

It is highly probable, therefore, that in the acute fever the microparasite runs through its life-history very rapidly and that the infection of fresh corpuscles takes place in the capillaries, where the latter are wedged in by infected corpuscles. Such plugs are frequently encountered in sections as well as teased preparations of various organs in which capillaries are traceable for some distance filled with infected corpuscles only. In the mild fever the slower development of the intra-globular parasite permits the infected corpuscle to circulate a longer time in the blood before it becomes a foreign body and is retained in the capillaries of the various organs. This retardation would account both for the presence of the young stage in the blood in the mild fever and its absence in the acute fever. The presence of infected corpuscles in the circulating blood in the latter type is, perhaps, more of an accident, and I am inclined to believe that, excluding the time immediately preceding death, the number depends somewhat on the amount of forced movements the animal is required to undergo. It is of importance to emphasize this point, for in many of the less severe acute cases it is often difficult to see a parasite even after prolonged search from day to day,

although the corpuscles may be disappearing at the rate of half a million a day.

If these views are in general true it becomes evident that any stasis of the red blood corpuscles in capillary areas may aid the micro-parasite in its multiplication. The great sensitiveness of the body in the beginning of the fever to corpuscular débris may cause it to react unduly with a high temperature, by which the growth of the micro-parasite is favored and its multiplication hastened. On the other hand, the gradual accustoming of the body to corpuscular débris in the circulation may account for the lower temperature in the relapse. The infected corpuscles continuing to circulate in the blood may be unable to grow rapidly, owing in part to the constant motion, in part to the absence of a high temperature, in part to causes to be discussed farther on.

In endeavoring to trace the life-period of the micro-parasite in the acute and in the mild fever, I was unable to find any clue whatever from the morphology of the parasite. The same forms appear day after day in monotonous succession. It has already been stated that the actual number of infected corpuscles in the circulation remains fairly constant during the disease in spite of the fall in the total number of blood-cells and the large numbers of fresh cells continually appearing. It is probable, therefore, that there are successive generations of micro-parasites formed during this period. If we take the number of infected corpuscles in the circulation as half a million, the fall in the total number per day, at one-eighth to one-fourth million, and the daily manufacture of new corpuscles at one-tenth to one-eighth million,[1] it would appear that the daily number of destroyed and infected corpuscles is nearly the same. If so, the life-period of the parasite would be about twenty-four hours. In the acute fever there are probably two or three generations per day. These statements agree very well with the high evening temperature in the mild disease and the continuous high temperature of the acute fever, if, as I believe, the fever in this disease is merely an expression of corpuscular débris in the body.

Before leaving this discussion concerning the retarded development of the micro-parasite I will briefly mention another still hypothetical phase of this subject. The presence of very minute, sharply defined

[1] These figures are based on estimates from a variety of cases.

bright bodies, frequently motile in the red blood corpuscles of cattle both in health and disease, already referred to, led me to presume that bodies of such a nature might, perhaps, be the earliest free-living stage of the micro-parasite. There are no definite facts to support this hypothesis. In the numerous examinations of fresh blood I simply noted the presence or absence of these bodies and their relative abundance. During the course of the investigation I observed one case, however, in which there was a manifest increase in the number of such intra-globular bodies accompanying the rise in the number of infected corpuscles. They were also remarkably active, and gave the impression of bodies moving with the aid of flagella or cilia. In this case the destruction of corpuscles was very slow while the number of cells infected by the coccus-like stage of the parasite was nearly half a million per c.mm. for one or two weeks. This association between the motile bodies and the micro-parasite led me to assume that there might be a further retardation of the intra-globular growth by which the motile stage may be prolonged and made prominent in the manner described. I present this hypothesis because I see no possibility of solving this interesting question at present, and the thought may at least be suggestive to others.

The theory of retarded growth of the intra-globular parasite as a result of the partial immunity of the host brings up the still undeveloped subject of immunity with reference to protozoan diseases. How the immunizing forces act we have no analogies to explain for us, and all that I may safely undertake at this time is to point out a few phases of the problem as they have forced themselves upon my attention.

If we take into consideration the phenomena of immunity, which are, so to speak, on the surface, we have facts enough to warrant the statement that immunity may be acquired. There is, first of all, the remarkable fact that animals from the enzootic territory may scatter the seeds of a fatal disease on pastures without becoming victims themselves. How is their immunity acquired? By heredity, or by repeated attacks, or by both factors combined? I had the good fortune to detect the mild fever in two calves born of Southern parents. This would indicate that in the enzootic region immunity is at least in part acquired through infection. Nearly all Northern

calves pass through the mild fever successfully, and only very few die from an acute attack. There must be some natural resistance, therefore, in young animals. This resistance combined with the effect of repeated attacks would account in a large measure for the immunity of adults.

As to acquired immunity in animals outside of the enzootic territory, a careful perusal of the experiments recorded in the monograph referred to will show that one acute or several mild attacks will protect from any subsequent fatal attack. If we turn to the internal phenomena, those revealed by the microscope and the numerical estimation of blood corpuscles, the line between immunity and susceptibility is somewhat less sharply drawn. For we find that even after several exposures there is still a slight but distinct fall in the number of corpuscles in the presence of infection, and what is still more remarkable, we find the infectious agent of Texas fever lingering indefinitely in the blood of apparently healthy and insusceptible cattle from the enzootic territory. It is present in such small numbers, however, that only occasionally can it be demonstrated by the microscope; and inoculation of such blood must be resorted to. This symbiotic relation between an otherwise fatal micro-parasite and an insusceptible host is, so far as I know, a new fact in the domain of infectious diseases, if the disease under consideration can lay claim to this title. The presence of the micro-parasite might be explained according to several different hypotheses:

1. The hypothetical swarm-spores in the blood may be ingested by leucocytes sufficiently trained to this function in the immune animal before the former are able to work their way into a red corpuscle. Those that escape successfully soon get beyond the chemotactic sense of the phagocytes by entering red corpuscles, where they may complete their development at leisure.

2. Or we may presuppose an increased resistance of the red corpuscle to invasion as well as toward dissolution when once invaded. The swarm-spore, unable to develop except in the red corpuscle, may become largely innocuous by this means of defence.

3. Another hypothesis would invoke the existence of a certain retarding influence on the development of the intra-globular parasite, which influence may co-operate with the resistance of the corpuscles to invasion. This retardation might be a result of chemical forces in

the blood, or it might be accounted for, as already stated, by the absence of any fever state of the host.

In explaining the presumed resistance of the blood-cell to invasion and destruction, we must assume an influence on the centres of corpuscle production which comes about simply by the increased exercise of their function. It is difficult to understand how an impression could be made in any other way.

Having now somewhat hastily disposed of those phenomena which may be referred to partial or complete immunity of the individual animal, we may turn briefly to those which are manifested in the diseased animal, as yet presumably without any forces that spring from complete or partial immunity to aid it in its struggle. At the outset one is struck with a marked monotony in the phenomena as presented in the blood during life and in the lesions of certain organs after death in the ordinary acute type of fever. Perhaps the main fact of interest is the quite sudden cessation of the fever and the disappearance of the parasite when the red corpuscles have fallen to 1.5 million. If the animal be young and if it reach this stage alive it is likely to recover. This sudden cessation of the disease proper seems to be due in part to the failure of the parasites to become mature before the corpuscles break down. For at the end of the acute fever the freed parasites, mainly in the intermediate stages, may be seen in enormous numbers in the kidneys. Again, when the number of corpuscles has touched the lowest point those now present are largely macrocytes, *i. e.*, new corpuscles in various stages of maturity, and are, perhaps, unsuited for the intra-globular life of the micro-parasite. The fully developed forms occasionally detected in red corpuscles in the interval between the acute fever and the relapse are no doubt the ancestors of the numerous parasites which reappear later. It may thus require a certain maturity of the corpuscles before the parasites can gain sufficient momentum to bring out secondary attacks It should be stated, however, that very rarely (in one case of prolonged fever) the large parasites are found within macrocytes of otherwise normal appearance, and that the minute coccus-like stage is not infrequently found in macrocytes. This could not well be otherwise, for the mild attack frequently keeps the number of corpuscles down to between one and two millions for one or more weeks, the regeneration meanwhile going on as fast as the

destruction. In such cases any but enlarged corpuscles are rare. This immaturity of the blood-cells cannot account for the characters of the mild relapse, for there are cases encountered in which the coccus-like stage of the parasite appears before the corpuscles have fallen much below the normal, and, hence, when macrocytes are still absent.

The cessation of the acute disease may thus be accounted for by immaturity of freed parasites and of blood-cells rather than by any reactive movement on the part of the host, such as phagocytosis or the microbicide action of the blood. It is true that freed parasites within leucocytes may be overlooked, because of the feeble staining capacity and the minute size of the former. Yet the many free parasites which collect in the kidneys after the acute attack indicate that they are inert bodies possessing little or no chemotactic power. The same inertness may be predicated of the infected corpuscles with reference to leucocytic activity. In the course of these investigations a small number of cases presented themselves with a very extensive inclusion of red corpuscles in phagocytes in the spleen pulp. This process goes on to some extent under other circumstances, as I have rarely missed a considerable quantity of spleen pigment, manifestly of intra-cellular origin, in healthy cattle. Yet it is very rare to see in such spleen any recent phagocytosis. In the Texas fever cases referred to this phenomenon was very pronounced. I have counted as many as twelve corpuscles in individual cells which had assumed a diameter of over 20 μ. In fact such cells appeared like a mass of corpuscles with only a trace of coarsely granular protoplasm around them. Only occasionally were such included corpuscles infected. It seems that these phagocytes simply take up what happens to be in their way, and the very pronounced stasis of blood corpuscles in the spleen (of which rarely more than 10 per cent. are infected) is very favorable to their activity. Any chemotactic power of infected corpuscles is not to be inferred.

If we turn to the leucocytes in the circulating blood the evidence of any active phagocytosis cannot be brought. There is, nevertheless, as might be expected, more or less disturbance of the leucocytes, which I am unable to formulate at present in spite of considerable work on this matter. All that I may say now is that the number of white cells is normal or somewhat diminished. There is more or

less fluctuation in the numerical relation between mononuclear and polynuclear leucocytes (exclusive of eosinophile cells). The latter seem to rise above the normal with the fever, and sink below the normal after it. The large mononuclear cells which greatly predominate (60 to 70 per cent.) in bovine blood are in part replaced by smaller cells allied to the lymphocytes of human blood, some of which may be the nuclei of hæmatoblasts. It is probable that more or less phagocytosis goes on where stasis exists in the capillary region all over the body in addition to what has been detected in the spleen pulp, for I have occasionally seen cells well filled with corpuscles in the liver and the kidneys. This in itself might be sufficient to account for the disappearance and active regeneration of leucocytes.

The same absence of any inflammatory phenomena is observed in the organs most markedly affected by the disease. In the liver we find a remarkably rapid and extensive fatty degeneration associated later on with a peculiar necrosis of the central zone of each lobule. The changes I am inclined to refer to the following causes rather than to any poison springing from the micro-parasite: Occlusion of the bile canaliculi with very thick bile, partial occlusion of the capillaries with infected corpuscles, and the sudden deprivation of oxygen by the daily loss of one-eighth to one-sixth of the corpuscles normally present. The enormous engorgement of the spleen is probably largely secondary to disturbance of the portal circulation, for the number of infected corpuscles seems to be too small to be credited with obstructing the capillary circulation to such a degree. Moreover, the appearance of the micro-parasites in the spleen pulp suggests unfavorable rather than favorable influences on their growth and multiplication. The kidneys, in spite of the engorgement, soon regain their normal condition if the animal survives Everything points to the inference that the reaction of the body moves within physiological limits and that the pathological elements which enter into the mechanism of bacterial diseases are absent. It might be claimed that in the acute diseases only negative chemotaxis is at work. If so we should see a swinging round into positive chemotaxis in the mild prolonged disease, as is the case with many bacterial diseases after partial immunity. But the blood does not present anything in the mild attacks which would lead us to infer any greater activity of the leucocyte elements.

In conclusion, I may briefly recapitulate those aspects of the subject which have a more direct relation to human pathology. The one upon which I have dwelt longest, the difference between the acute and the mild disease, has an important bearing on the interpretation of irregular malarial fevers and the relation of their respective micro-parasites to those of the regular types. The question of progressive immunity as a possible modifier of these diseases has not been brought up heretofore, so far as my information goes.

The comparative poverty of the circulating blood in infected corpuscles in the acute disease and the possibility that the true cause might entirely escape observation even at the autopsy, if death took place a few days after the subsidence of the fever, should not be lost sight of in the investigation of diseases of still unknown etiology.

In the regeneration of the red blood-corpuscles after Texas fever, the following points are of interest in the comparative study of the blood:

1. The appearance of enlarged corpuscles (macrocytes) when regeneration begins. This does not set in until after the subsidence of the high temperature in the acute fever. In the mild fever it regularly begins when the number of corpuscles has fallen to three millions.

2. The appearance of macrocytes which take a feeble stain or show a number of stained granules on their disk with methylene blue when the number has fallen below two millions.

3. The regular appearance of hæmatoblasts when the number is below one and one-half million, and their occasional presence before this level is reached.

4. Poikilocytes are absent. Microcytes extremely rare (one case in 150 or more).

The relation of the ecto-parasite of Southern cattle—the cattle tick (*Boöphilus bovis*, Riley, Curtice)—to the disease, I have refrained from discussing, as it is fully brought out in the monograph referred to. Cattle from a certain Southern belt of our country drop ripe female ticks on Northern pastures where the native cattle graze apparently unharmed until suddenly, after a period of fifty to sixty days, a fever attacks the herd, to which all may succumb within a few days. The unobtrusive transfer of the micro-parasite from the blood of Southern to Northern cattle is effected by the young generation of

ticks. The ripe females which drop from Southern cattle lay their eggs, the young emerge after a time and crawl upon the cattle. When they have pierced the skin the disease appears. In what manner the micro-parasite passes from the old to the young ticks, or what form the former assumes in its simple transfer or its migration, it is impossible to state at present, and I shall not weary you with hypotheses. The agency of parasites in transferring the microbes of protozoan diseases should henceforth receive more attention than it has hitherto received. In the disease before us the evidence is very strong that the ecto-parasite is, if we accept rarely occurring accidents, the only transmitter of this disease to Northern animals. Perhaps the mysterious distribution of some endemic diseases may be due to a similar agency.

There is one other question which it may be superfluous, perhaps, to consider a question any longer, but which must not be lost sight of too soon. I refer to the etiological relation of protozoan parasites to the diseases with which they are associated. In the course of these investigations I frequently returned to the problem whether the micro-parasite of Texas fever might not be simply a concomitant. The presence of minute motile bodies within the red corpuscles of healthy cattle led me for a time to take the position that, perhaps, the introduction of some poison by the young cattle tick enabled these problematic organisms to start up and, after a sufficient momentum was gained, to overwhelm the blood by a rapid multiplication. There are, however, a number of facts directly opposed to this hypothesis. Thus the invariable appearance of Texas fever after the injection of blood from Southern cattle from the permanently infected territory long after they had been deprived of ticks, hardly admits the theory of a poison. To suppose that healthy cattle carry in their blood a fatal organic poison otherwise than as a living organism, requires a better array of facts from other infectious diseases than we possess to-day. Again, the important feature of the relapse certainly favors the parasite as the true cause. If an organic poison should have such a prolonged exhausting influence extending over months, our conception of infectious diseases would require modification nothing short of revolutionary.

Another fact in favor of the microbic cause is the peculiar restriction of this disease to cattle, so far as known. Sheep, guinea-pigs,

rabbits, and pigeons are insusceptible. From twenty-five to three hundred times the dose per body-weight of infectious blood sufficient to kill cattle had no effect on guinea-pigs. This peculiar limitation of the virus stamps it as highly organized, very specially adapted. Only the intra-cellular protozoon will satisfy these conditions.

Finally, these investigations do not throw any additional light on the possible agency of protozoa in producing an active proliferation of cells such as is manifested in the different forms of cancer. So far as the evidence goes it is totally negative. The Texas fever parasite is simply a destroyer of cells. The same I may say of several other cell-parasites to which I have given some attention. Yet there may be a wide range of metabolic activity belonging to different classes of protozoa which may put to shame any premature generalizations. We have learned, within ten years, to recognize a great variety of cell activities among the morphologically quite monotonous group of bacteria, and it may be reasonable to expect as much from the morphologically very divergent parasitic protozoa.

It still remains for me to express my obligation to F. L. Kilborne, B.V.S., and E. C. Schroeder, M.D.V., without whose efficient cooperation this work could not have been carried out.

DISCUSSION.

DR. WELCH: Dr. Smith has very kindly shown me his specimens at different times, and I am quite familiar with the development of his work and am extremely interested in his results. The etiology of Texas cattle fever has become, through Dr. Smith's researches, probably clearer than that of any other protozoan disease. We now know not only the character of the micro-organism inside the body of the animal, but also the media of development outside of the body, in the cattle tick. Dr. Smith is to be congratulated upon such an important contribution to science, which is an illustration of the value of governmental aid to solving a problem of both scientific and economic importance.

THE BACILLUS PYOCYANEUS PERICARDITIDIS.

By HAROLD C. ERNST, M.D.,
OF JAMAICA PLAIN, MASS.

Much attention has of late years been given to the effects of the cultures and the products of growth of the bacillus pyocyaneus, especially in anthrax. At various times authors have announced the isolation of bacteria very closely resembling this one, but the only one that seems to have gained a permanent place in literature is the B. pyocyaneus β of P. Ernst, which was described by him a number of years ago. The differences as given are not marked, and Gessard is not inclined to acknowledge that they are due to more than temporary conditions, which appears the more justifiable for the reason that these differences are largely simple variations in degree and intensity of color-production.

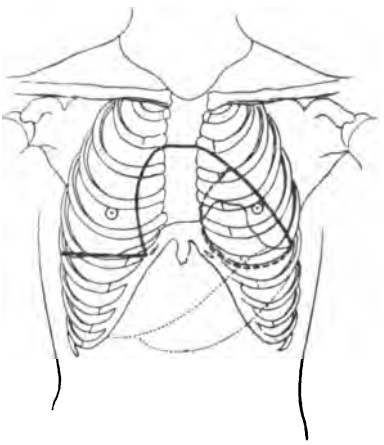
It is not only upon differences in color-production that the separation of the organism described in this paper depends, but upon difference of size as well, and the position taken appears to be justifiable because these differences have been found to be constant through a long series of cultures and controls.

The material from which the bacillus was originally obtained was placed in my hands by Drs. Councilman and Whitney, and came from a case in the service of Dr. F. C. Shattuck at the Massachusetts General Hospital, having been sent into the house from my service in the Out-patient Department. I am indebted to Dr. Shattuck for the following abstracts from the Hospital Records:

Oct. 26, 1892. J. E. H., aged forty-seven years, married, laborer, Demerara. No family history. Denies venereal disease. Pneumonia eight years ago; "malaria" three years ago, with no periodicity. Signs of effusion about the heart (see diagram), showing dull area to right of sternum, and included in heavy black line. To the right of the sternum was heard a to-and-fro friction murmur, high-pitched and well marked. Respiratory murmur not

heard over the dull area. Fibrillary twitching of the left pectoralis major. Cardiac sounds more and more muffled proceeding toward the apex.

Nov. 18. Examination of the lungs absolutely negative. Some cough at night with absolutely no expectoration.



Oct. 27, 1892. Line of effusion. Systolic murmur within broken lines.

19*th.* Pericardium tapped in fifth interspace just inside the line of flatness. About a pint and a half of fluid removed, and sent to Dr. Whitney for examination. Reasons for tapping: 1, increasing and disproportionate rapidity of respiration as compared with the pulse and temperature curves: 2, increasing loss of flesh and strength; 3, non-absorption of fluid in pericardium; 4, sudden attack of weak heart and embarrassed respiration.

26*th.* Tapped again. Some of the fluid sent to Dr. Councilman, who reports plenty of tubercle bacilli and a new bacillus which liquefies gelatin.

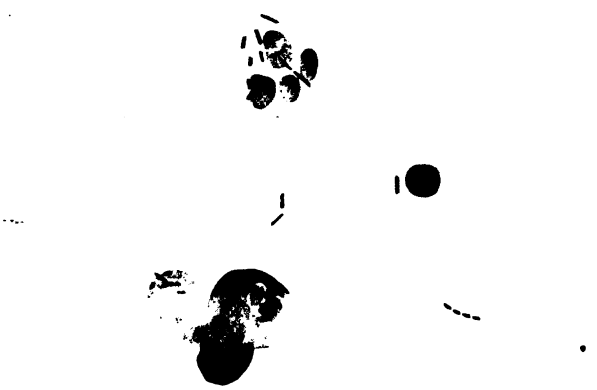
Dec. 17. Tapped a third time. One quart and one gill removed.

March 5. Tapped in sixth interspace one-half inch outside of nipple, and a pint of yellow turbid fluid obtained.

12*th.* Eloped (and could not be traced).

As will be seen from these brief extracts, the case is one of extreme interest from a purely clinical point of view. It will be reported by Dr. Shattuck in connection with others. That part of it which should be spoken of here concerns only the gross appearance of the fluid removed at the various tappings and the micro-organisms it contained.

The results of the first and the last tappings I did not see. Those of November 26th and December 17th were a fluid, clear and amber colored



Cover-glass preparation of pericardial fluid, stained by the Koch-Ehrlich method. The red rods are bacilli of tuberculosis. The blue rods are the bacillus pyocyaneus pericarditidis. (Comp. oc. 12. Apochrom. obj. 1.30. Camera lucida.)

faintly alkaline, and depositing a slight sediment only after standing. There was no odor, but a very large per cent. of albumin—the fluid coagulating very readily by heat, and when sterilized forming an apparently favorable medium for the development of the bacillus found in it.

The microscopic examination by Dr. Councilman showed a number of the bacilli of tuberculosis, and a second bacillus, whose arrangement in the cells of the fluid attracted attention, because of its unusual character (see Plate).

At my request, a portion of the fluid was given to me for bacteriological analysis. Plate-cultures in gelatin, and needle-cultures in blood serum showed the presence of no other organism than one corresponding in its appearance under the microscope to that seen in the original fluid. Such an examination was made the second time, of the fluid removed upon December 17, with the same result. From these cultures a long series of tests have been made upon a large number of different media and under different conditions of temperature.

Every step in the investigation has been checked by and compared with cultures of the bacillus pyocyaneus derived from the following sources:

1. My own laboratory culture, which came originally from the Hygienic Institute of Berlin, and has been under constant cultivation ever since.

2. From the laboratory of Johns Hopkins University, sent to me by Dr. Welch, he being not quite certain of the origin of the culture.

3. From the laboratory of the College of Physicians and Surgeons, sent to me by Dr. Cheesman at the request of Dr. Prudden, and coming originally from Prague.

4. From the Army Medical Museum, given to me by Dr. Gray, and of uncertain origin.

Inasmuch as cultures from all these sources substantially agreed in gross appearances and under the microscope—minor variations of growth and intensity of color-production being left out of account (for these were more in one at one time, and in another at another)—and at the same time, inasmuch as they all differed in the same way and under the same conditions from the new bacillus, the conclusion is irresistible that this organism is an undescribed variety, and differs from the bacillus pyocyaneus of Gessard by well-marked and constant characteristics.

The results of the culture experiments have been tabulated for

convenience sake, and the description of the B. pyocyaneus of Gessard and of the B. pyocyaneus β of P. Ernst are added for ease of comparison.

These are the only two organisms with which the bacillus pyocyaneus pericarditidis is likely to be confounded.

BACILLUS PYOCYANEUS PERICARDITIDIS.

ORIGIN. Pericardial fluid, containing also bacilli of tuberculosis.

FORM AND ARRANGEMENT. Small straight bacilli, with rounded ends, three or four times as long as broad, and on most media slightly larger than the B. pyocyaneus of Gessard, occurring within the cells in the original fluid, and sometimes showing two or three end to end, but never observed in long chains.

MOTILITY. Actively motile in hanging-drop culture. No cilia or flagella have been demonstrated.

GROWTH. *Gelatin: Plates.*—Colonies appear at the end of 36–48 hours, as fine white points in interior, and upon the surface of the medium; edges are sharply defined; soon there appears a circular zone of liquefaction, finally passing through the stratum of the medium with the colony at the bottom. Under a low power the centre of the colony may be of a brownish color. On the second day a greenish tinge may be seen about the individual colonies on the surface which spreads through the entire medium. The plates may always be distinguished from those of the B. pyocyaneus of Gessard by the *bluish-green* when contrasted with the yellowish-green color of this latter.

Gelatine: Needle cultures.—At end of 24 hours a small saucer-shaped depression of liquefaction at upper end of needle track, which gradually spreads and deepens until the liquefaction extends straight across the tube and about half-way down the needle track. A bluish-green fluorescence appears about the liquefied portion at the very upper part of the gelatin, later changing into a yellowish-green. The colony is deposited as a yellowish heavy sediment at the bottom of the liquefied portion, the upper part of which is clear. A small whitish growth occurs along the remainder of the needle track. Old cultures, in which a certain amount of evaporation has occurred, assume a very dark greenish-black color.

Agar-agar.—Along the needle track appears a *flat*, dry colony of a dirty grayish-white color spreading out upon each side of the needle track and growing, at first, upon the surface of the water of condensation, later depositing a white sediment at the bottom. From the first there may be detected, by reflected light, a metallic lustre on the surface of the colony in places, which metallic sheen later spreads over the whole colony and furnishes a marked differentiating point. In addition to this, within 24–48 hours at 37° C., there appears a green fluorescence throughout the whole of the medium, which increases slowly to a marked *bluish-green* color, and never assumes the nut-brown of the B. pyocyaneus of Gessard upon the same medium. The colony is not especially viscid.

Potato.—There appears a reddish-brown colony along the needle track, elevated and moist, and pretty cloudy, confined to the line of the needle. Presents no change of color upon touching with needle, but certain specimens (as do some of the B. pyocyaneus) develop later a heavy green color extending over the whole surface of the potato, which later changes almost to black.

Bouillon.—Twenty-four hours at 37° C. gives a growth, especially on the surface, which is a wrinkled scum; no cloudiness of the bouillon, and a very

faint greenish fluorescence 1 cm. below surface. At this time differs from the B. pyocyaneus of Gessard, in that the latter shows cloudiness of the medium all through. Later the same cloudiness appears in bouillon cultures of this new bacillus, together with a whitish sediment deposited at the bottom of the tube, and then the cultures are indistinguishable from each other. Same changes, but slower, occur at room temperature.

Peptone.—1, 3.5, and 6 per cent. solution. Twenty-four hours at 37° C. gives faint bluish tinge at upper edge of medium with very faint cloudiness; later (in one to two weeks) there forms a marked scum upon surface that is difficult to break up by shaking, and the whole medium assumes a grass-green color of more or less intensity and not seen on other similar bacilli. The shape and size of the organism, under the microscope, differs very markedly in this medium from any other bacilli examined. Same changes to be seen at room temperature, but more slowly.

Egg-Albumen. (*Plain*).—Twenty-four hours at 37° C., yellowish-white, very profuse growth all along the needle track; yellowish-green spreading out from it almost to sides of tube, and in the condensation water as well. The growth has no especial distinguishing characteristics. Irregular liquefaction occurs, but the growth at no time differs in any marked way from other varieties of the B. pyocyaneus.

Blood-serum.—Twenty-four hours at 37° C. shows flat, moist colony with bluish-green fluorescence in its neighborhood. Liquefaction begins early and goes on slowly until complete in from one to two weeks, with an increasing intensity of color which becomes markedly blue, and eventually almost black.

Milk.—Behaves as do the other bacteria.

Behavior to Temperature. Grows at 15–25° C., slowly; much more freely at 35–38° C., when it produces the color more quickly.

Rapidity of Growth. Moderate.

Spore-production. Not observed.

Need of Air. Does not grow under mica. Facultatively anaërobic, but does not produce color except with free access of oxygen.

Gas-production. Produces faint foul odor.

Behavior to Gelatin. Liquefies gelatin slowly.

Color-production. Produces a bluish-green color which in old cultures changes almost to a black. Upon the addition of acids (both vegetable and mineral) to cultures the color changes to red, and upon the addition of alkalies a bright grass-green appears. This reaction is best seen in bouillon and gelatin cultures, but occurs in other media as well, notably blood-serum.

Behavior to Aniline Dyes. Stains easily and well with any of the aniline dyes usually employed, and by Gram's method.

Microscopic Appearances in Different Media. Under the microscope its general appearance on various media is of a rod larger than the B. pyocyaneus. In peptone cultures this difference is very marked. In this case, the B. pyocyaneus tested appeared as very short oval bacilli, almost like micrococci, while the new bacillus showed as a long fine rod, from four to six times as long as broad, about one-half the diameter of a red blood-corpuscle, and arranged sometimes two or three end to end. These same cultures transferred to gelatin became indistinguishable from each other in size.

Pathogenesis. Injections of small quantities (0.5 cm.) of a bouillon culture twenty-four hours old into the abdominal cavity of rabbits and guinea-pigs, killed 50 per cent. in from twenty-four to thirty-six hours. Autopsy showed general congestion of abdominal viscera, slight effusion into the peritoneal cavity, and cover-glass preparations and cultures showed the bacilli in the effusion in the abdominal cavity, as well as in the blood from the heart and various organs.

BACILLUS PYOCYANEUS. (GESSARD.)

ORIGIN. In "green" pus. Really the green color only appears after exposure to oxygen, so that the pus itself is never green as a result of growth of the organism.

SHAPE AND ARRANGEMENT. Short fine rods; often can be confounded with cocci.

MOTILITY. Actively motile.

GROWTH. *Gelatin: Plates.*—After two or three days the entire plate has taken on a clear green color (grass-green), the surface colonies liquefying the gelatin in a funnel shape. Under a low power the deeper colonies appear round and somewhat yellowish, with clear, strongly refracting granular edges.

Needle cultures.—After twenty-four hours the upper surface of the gelatin is liquefied in a funnel-shaped depression with fluorescent coloring (grass-green) of the upper surface. The liquefaction later extends straight across above the solid portion to the sides of the tube, and the whole gelatin takes on a beautiful fluorescence.

Agar-agar.—Moist greenish-white layer along the needle track and spreading out on each side, and the whole agar becomes colored with a diffuse, beautiful fluorescence (grass-green), which later turns to a nut-brown color.

Potato.—Dry nut-brown elevated colony along the needle track. With ammonia it takes on a green, with acids a red color.

Milk.—Produces a yellowish-gray layer at upper part; produces casein, and peptonizes it with help of ammonia

BEHAVIOR TO TEMPERATURE. Grows well at summer temperature.

RAPIDITY OF GROWTH. Grows rapidly.

SPORE-PRODUCTION. Not observed.

NEED OF AIR. Will not grow under mica plates.

GAS-PRODUCTION. Not observed.

BEHAVIOR TO GELATIN. Liquefying.

BEHAVIOR TO ANILINE DYES. Produces blue pigment, pyocyanin. Stains easily with ordinary aniline dyes and by Gram.

PATHOGENESIS. Guinea-pigs inoculated in abdominal cavity are killed (Koch). Rabbits inoculated in blood-current live.

BACILLUS PYOCYANEUS β. (P. ERNST.)

Zeit. f. Hyg., Bd. ii. S. 36, ii.

ORIGIN. In the pus of gray-colored dressings.

FORM AND ARRANGEMENT. Small, very slender rods, not producing chains, but only two or three together at the most, probably possessed of cilia.

MOTILITY. Actively motile.

GROWTH. *Gelatin: Plates.*—Colonies never sharply defined, but with delicate radiating threads, which are always visible, until by liquefying in circular form the colony sinks to the bottom in an irregular mass. The neighboring portion of the medium is colored green.

Needle cultures.—In the shape of, at first, a round and soon a pointed, deeply widening champagne-glass shaped liquefaction with a slowly appearing green coloring of the medium.

Agar-agar.—As a greenish white but dry layer along needle track, with green coloring of the agar.

Potato.—From a fawn to nut-brown dry colony, which turns gray when touched with the platinum needle. The "chameleon" phenomenon. Different from B. pyocyaneus *a*.

Bouillon.—A thin spider's-web-like growth on surface, which, by shaking,

easily collects into skeins and sinks with difficulty. The upper part of the bouillon is colored green.

Milk.—Green color at upper surface; rapid coagulation and energetic peptonizing of the casein.

BEHAVIOR TO TEMPERATURE. Grows at 15–25° C., but luxuriantly at 35–40° C., when it produces the green color more quickly.

RAPIDITY OF GROWTH. Grows with moderate rapidity.

SPORE-PRODUCTION. Not observed.

NEED OF AIR. Strongly aërobic.

BEHAVIOR TO GELATIN. Gelatin is rapidly liquefied and turned into a fluid as thin as water.

COLOR-PRODUCTION. Produces a yellowish-brown color, which very easily changes by oxidation into a dark-green. It is sufficient to shake the cultures, thus bringing in the oxygen of the air, to produce a dark-gray color. Old cultures turn a strong black-brown.

PATHOGENESIS. Not known.

SUMMARY.

The essential differences between this bacillus and those with which it has been possible to compare it are, therefore, as follows:

I. *Macroscopic.*—1. The *bluish-green* tinge of the gelatin in plate-cultures as seen by reflected light, as distinguished from the *yellowish-green* tinge of the others.

2. The dryness and metallic lustre of fresh cultures and the bluish-green color, by reflected light, of old cultures upon agar-agar, as distinguished from the moist elevated fresh colonies and rust-brown color by reflected light of old colonies of the others.

3. The greenish color of old colonies in peptone solutions of varying strength, as distinguished from the bluish color of the other bacteria tested with it.

4. The very much greater rapidity and intensity of the reaction of gelatin and bouillon cultures to acids (red color) and alkalies (grass green).

II. *Microscopic.*—The variations in its appearance under the microscope, as follows:

1. Preparations from gelatin cultures—indistinguishable.

2. Preparations from peptone cultures show long slender rods, as contrasted with short oval ones.

3. On other nutrient media, its general average as a larger rod, which can be made out by actual comparison, but is hardly subject to measurement. This difference can be seen, however, in preparations from egg-albumen, bouillon, blood-serum, and potato. Only upon gelatin and agar is there no appreciable difference.

It appears, therefore, justifiable to conclude that we are dealing with a distinct variety of organism, resembling in many respects the B. pyocyaneus, but perfectly separable from it.

DISCUSSION.

DR. ABBOTT: From the description given it seems to me that in this bacillus described by Dr. Ernst we have another addition to make to the group of green-producing micro-organisms. Some of its characteristics are very different from those common to the ordinary green-pus organism.

DR. THEOBALD SMITH: I would like to ask what difference there is between this bacillus and the ordinary *bacillus fluorescens liquefaciens*, which is frequently encountered in the organs of animals affected with ulceration of the intestines. From the description given I see no very marked differences. I have not myself examined the bacillus pyocyaneus, and consequently cannot say whether they are alike or not.

DR. ABBOTT: The essential difference that I note between the organism with which Ernst has been working and the organism of which Dr. Smith has spoken is the production of the blue-green color upon which Dr. Ernst lays special stress. If my memory serves me right, the saprophyte referred to by Dr. Smith produces a green color; but I have not noticed the production of a blue color with ultimately the production of almost a black color, as Dr. Ernst states his organism does.

DR. SMITH: I have seen all variations in the color-producing power of this saprophyte, and in some cases the color was a very dark green.

DR. WHITTAKER: The most important thing would be to establish in regard to this bacillus the uniformity with which it is found in cases of pericardial effusion. Of course, this paper is based upon a single observation of a single case of pericardial effusion. One would think that the vomicæ in phthisis, which are in free communication with the air, would contain all sorts of organisms besides the bacillus tuberculosis; but the truth is that generally one or a few predominate, and in most cases the streptococci. The most interesting thing in connection with this case would be to establish whether it deserves to stand in any way as a causative factor in the production of pericarditis. Everyone knows that in pleural effusions and pericardial fluid micro-organisms are present very sparsely, and it is sometimes only by centrifugal precipitating apparatus that we can get any micro-organisms at all. If we could find this pyocyaneus organism, whose individuality seems to be established, more

in connection with pericardial effusions it would certainly be a valuable contribution.

DR. ABBOTT: I will say just a few words on the point raised by Dr. Smith in regard to the variation in color. It is very likely, from some experiments I have had under my observation lately, that among the green-producing saprophytes existing under the name bacillus fluorescens there are several organisms, usually grouped together, but which have minor points of difference by which they can be distinguished one from another.

THE RESULTS OF INOCULATIONS OF MILCH COWS WITH CULTURES OF THE BACILLUS DIPHTHERIÆ.

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During the past twelve or fourteen years there have appeared at odd intervals several epidemics of diphtheria that are believed to have originated with the milk used by the persons affected. This circumstance has led to their being known as "milk epidemics" of diphtheria, and by some individuals the milk is believed to have been capable of producing the disease at the time it was obtained from the cow, and not, as is more generally the opinion, that it had become infected on its way from the cow to the consumers. In at least three outbreaks in England, there was no evidence that the milk had been infected by those through whose hands it had passed, and in consequence, suspicion was directed to the cows from which it had been obtained. With the idea of determining how far this suspicion rested upon a possible basis, Klein (1) endeavored to study the reaction of milch cows to the virus of human diphtheria. With this in view, he inoculated each of two healthy cows subcutaneously over the left shoulder with one cubic centimetre of a bouillon culture of the bacillus diphtheriæ. On the second and third days after inoculation the temperature in each rose a degree, centigrade, and there was diminution in the amount of food consumed, but by the fourth day both cows were again in an apparently normal condition.

On the second day following the inoculation there appeared beneath the skin at the seat of operation, a localized, soft, painful swelling, which continued so, and by about the eighth or tenth day was as large as one's fist. During the second week the tumor gradually

diminished in size, became harder and more circumscribed, and could be readily moved about over the underlying tissues. During this time (the second week) both cows became affected with a cough, and auscultation and percussion revealed the presence of decided thickening, and bronchial respirations in the upper portions of both lungs.

On the twefth day Cow No. 1 ceased taking food and died on the night of the fourteenth day. On the twenty-third day Cow No. 2 showed evidence of approaching her end, and she was killed on the twenty fifth day.

After the third day from the date of inoculation neither animal had a rise of temperature. Between the sixth and the tenth day after inoculation in Cow No. 1, and the fifth and the eleventh day in Cow No. 2, there appeared upon the udder and teats a most peculiar eruption, appearing at first as injected papules, which on the following day became surrounded by a small vesicle, which in time was limited by a zone of reddened skin. The skin beneath the vesicle was indurated. The vesicles contained clear lymph. In ten days after their first appearance the vesicular eruption had become pustular; in another day the pustules were covered with a brown scab. During the two or three days following, the scab enlarged and became brown-black in color. If at this time a scab was removed, a bloody indurated ulcer remained. After two or three days more the scabs dropped away spontaneously, leaving a dry and healed scar; the entire process taking usually from five to seven days. The smallest of these points of eruption were about 0.5 cm. in diameter, the largest from 1.0 to 1.25 cm. in diameter. They were always round or roundish in outline, and in the vesicular and pustular stages some of them exhibited a dark centre. None of them were umbilicated. At the autopsies upon these cows essentially similar conditions were found in both.

In the neighborhood of the left shoulder, at the seat of inoculation, intimately attached to the skin, was found a dense mass which formed, with the subcutaneous and muscular tissues, a peculiar circumscribed tumor, freely movable over the underlying structures and surrounded by an œdematous and hemorrhagic zone. Upon transverse section it was seen to consist of numerous thin and thick lamellæ of necrotic tissue, between which transverse section of muscle fibres could be seen. In the neighborhood of this tumor was a swollen, œdematous

lymph-gland, which was somewhat hemorrhagic in its periphery. Adjacent to this gland were numerous smaller glands of a dark-red color. Upon microscopic examination both the peripheral and central portions of these glands contained much extravasated blood.

Both lungs in the upper portion, and also the middle lobe of the right, and the lower lobe of the left, were markedly hyperæmic. Groups of lobules were found that were of a deep-red color, injected, œdematous, and sank in water. The septa between the lobules were œdematous. The sub-pleural lymph canals were seen to be filled with clear (Cow No. 1), and with blood-stained (Cow No. 2) lymph. Upon section through the upper lobes the bronchi were everywhere seen to be surrounded by a dense gray exudate which faded off into the surrounding tissues. The bronchial glands were swollen and œdematous.

On the surface of the liver were numerous irregular, gray or brownish spots, which proved to be necrotic areas of liver tissue. Both kidneys were hyperæmic, with also gray areas of fatty degeneration in the cortical substance. The visceral pericardium contained areas of extravasated blood, both punctiform and conglomerate.

The microscopic examination of horizontal sections of the tumor from the seat of inoculation showed a process characterized by white, necrotic septa, which formed a picture similar, in all essential respects, to that seen in sections of membrane from human diphtheria. The muscle bundles between the septa were, at many points, in advanced necrosis. Everywhere in the septa and necrotic tissues appeared masses of diphtheria bacilli, either singly in small or, as in the tumor from Cow No. 2, in large ball-like masses.

Muscle fibres near the necrotic tissues were here and there, either in part or entirely, supplanted by masses of bacilli. In many points the gradual penetration of the dying muscle-substance by the bacteria could be readily made out.

From the tissues of the tumors from both cows cultures were made. In not one of twenty-four smear tubes was anything but pure cultures of a bacillus obtained, which in morphological and cultural peculiarities could not be differentiated from the bacillus diphtheriæ obtained from man or from guinea-pigs. Cultures from the lungs, kidneys, and heart's blood were negative. From the lymph of the vesicles on the udder, it was possible to demonstrate

the bacillus diphtheriæ, not only in cover-glass preparations, but also by culture methods.

Bacteriological examination of the milk made on the fifth day after inoculation, the date at which the eruption first appeared upon the udder, resulted in the appearance of colonies of the bacillus diphtheriæ on three out of four slanted gelatin tubes, upon the surface of each of which $\frac{1}{16}$ c.c. of the milk from Cow No. 2 had been deposited. On three subsequent occasions, the tenth, eleventh, and twenty-fifth days after inoculation, the milk was again examined, but no colonies of the bacillus diphtheriæ could be found.

In order to demonstrate the contagious nature of the eruption on the udders of these cows, two calves were inoculated with the contents of the vesicles and pustules. The inoculations were made in the way commonly practised in vaccinating calves, viz.: into a small pocket in the skin of the abdomen.

Between the sixth and the seventeenth days both calves developed an eruption in all essential respects identical with that upon the cows from which they had been inoculated. Calf No. 2 developed a cough, and Calf No. 1 a mucous discharge from the nostrils. On the twenty-fourth day both calves were killed. No evidence of the eruption could at this time be found. The upper lobes of both lungs of both calves, and the upper part of the adjacent lobes were dark-red in color, solid, and sank in water. Upon section the bronchi were surrounded by a dense gray tissue. The medullary substance of both kidneys was hyperæmic, while the cortical substance was grayish-white and conspicuously fatty.

This is, in short, the description given by Klein of the results of his inoculations of milch cows with cultures of the bacillus diphtheriæ. The particular object of Klein's experiments was apparently less to study the pathological lesions produced in these animals by the inoculations, than to determine if it was possible, through the inoculation of cows with the virus of human diphtheria, to demonstrate its presence in their milk. The experiments were suggested to him by an opinion then extant in England, that in several of the milk epidemics of diphtheria (particularly those in the north of London in 1878, in Yorktown and Camberwell in 1886, and in Enfield and Barking in 1888) the infective agent had reached the milk through the cow, and had not been introduced into the milk through human agency—an

opinion of sufficient gravity to call for all light that experiment is capable of throwing upon it. This opinion is probably influenced by the erroneous impression that the pseudo-membranous process in the throat, with which calves are at times affected, is identical with diphtheria in the human being.

In an address made by Löffler, at the International Medical Congress, in Berlin, 1890, in the Section on Hygiene, he expressed the opinion that the results of these experiments were of a doubtful nature, and that the subject was of such importance as to require confirmation from other sources. It was through this address that my attention was called to the experiments of Klein, and as opportunity has presented during the past winter to repeat these inoculations, I have done so. It is the results of these experiments that I propose to embody in this paper.

Cow No. 1. *Inoculated March* 8, 1892; *died March* 24, 1892.—On March 8, 1892, I inoculated into the tissues of the right shoulder of this cow, 1 c.c. of a bouillon culture of bacillus diphtheriæ, the virulence of which was at the same time tested upon a guinea-pig, the latter dying after the usual time and with the tissue changes common to these animals when under the influence of the virulent bacillus diphtheriæ. This cow had for some time prior to inoculation been tuberculous, and at the date of inoculation was markedly so.

Before inoculation careful examination was made of her udder and teats, and they were found to be normal, no excoriations, blebs, ulcers, or anything else of an unusual character being present.

At this time her temperature was 102° F., and she had been having a tolerably regular evening exacerbation of about a degree higher. The daily range of temperature after inoculation will be seen by reference to temperature chart No. 1.

At no time while under observation did this cow show any marked constitutional disturbances, beyond a rise of temperature, that might have been looked upon as a result of the inoculation. She was never "off her feed," and beyond a cough showed no signs of discomfort. Her udder and teats were frequently examined, but at no time did we discover anything in the form of an eruption.

For three or four days after inoculation there was tenderness over the point at which the needle had been introduced; this was accompanied by a slight swelling which rapidly diminished in size until ultimately it gave to the hand the sensation of a dense, flat nodule of about 3 x 5 cm. It was firmly attached to both the skin and underlying tissues, so that it could not be easily moved about. Beside these points no noticeable alteration in the condition of the animal could be made out. She died November 24th, sixteen days after having been inoculated.

At autopsy the tuberculous process was found to be very widespread. The lungs were little more than caseous masses and conglomerate tubercles. The bronchial glands presented a condition of caseation. The pleuræ were studded with tuberculous masses, likewise the peritoneum. The tuberculous process in the pleuræ and lungs was so advanced that no attempt was made to study the changes described by Klein in these organs, as resulting from his inoculations of cows with the bacillus diphtheriæ. The udder was carefully examined externally for evidences of pre-existing eruption, and internally by means of parallel incisions made at a distance of three-quarters of an inch from one another throughout the entire gland, but no abnormal condition was detected.

TEMPERATURE CHART 1.

Cow No. 1. Inoculated with bacillus diphtheriæ November 8, 1892; died November 24, 1892.

At the seat of inoculation was found a flat, tough mass, more or less adherent to both skin and underlying tissues, though with a little effort it was easily separated from both. This mass measured approximately 2 x 3 x 0.5 cm. This oval bit of tissue was unusually dense, and it was only with much difficulty that the point of a scalpel could be introduced into it. It presented nothing characteristic to the naked eye. It was simply a white, fibrous-looking mass.

Under proper precautions an incision was made into the tumor with a knife that had been sterilized in the flame and allowed to cool. From the faces of the incision scrapings were made, and with these scrapings blood-serum tubes were inoculated; Petri plates of glycerin-agar were made, and slant tubes of glycerin-agar were also inoculated. By none of these methods could we demonsrtate the presence in the tumor of living diphtheria bacilli.

The tumor was preserved in absolute alcohol, and when properly dehydrated, a portion was imbedded in celloidin, while from another portion sections were cut without imbedding. Examination of these sections revealed a most interesting condition.

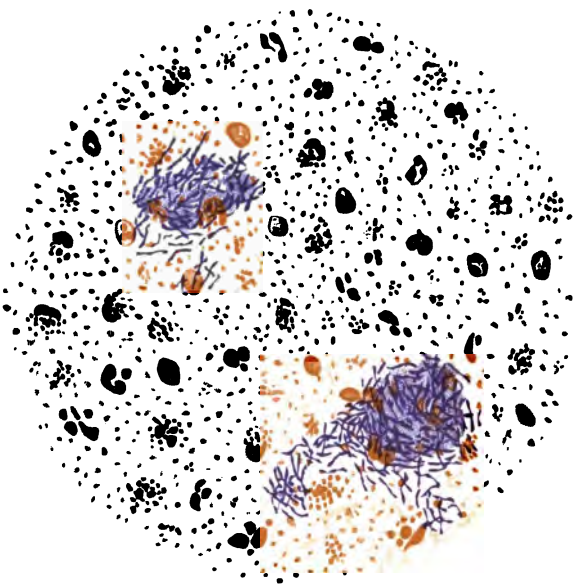
Upon *microscopic examination* the tumor was seen to consist of two portions, a peripheral zone of newly formed connective tissue, and an irregular central

area advanced in a condition of necrosis. In this central area, which formed the bulk of the tumor, could be seen muscle fibres and connective tissue in various stages of death. At many points the destructive process had advanced to such an extent that, beyond a reticulum of fibrin with here and there fragments of cell nuclei, but little of the original structure could be made out.

The epidermis, where preserved, was quite normal. Just beneath it was a layer consisting of connective tissue and muscle containing an excess of nuclei. The fibres and bundles of connective tissue were pressed apart, evidently the result of œdema. Beneath the layer of muscle was a thicker band of connective tissue which also presented an excess of nuclei. The nuclei in the layers just beneath the epidermis were of two kinds, polyform leucocytes and connective-tissue nuclei. The leucocytes were sometimes aggregated into masses which lay between and in the tissue elements. The lymph spaces of the tissues were dilated and contained numerous leucocytes. The small veins were sometimes almost plugged with them, yet many still contained a few red blood-corpuscles. Where the leucocytes were present in greatest numbers the tissue elements about them did not stain. The increase in number of connective-tissue nuclei was particularly in the intermuscular septa in the subcutaneous tissues; they were round, elongated, or slightly irregular, and some were fragmented. There were, moreover, polynuclear leucocytes in these septa.

The muscle fibres themselves in these situations were swollen and presented a hyaline aspect; striations could not be found in them, and in a few instances an appearance was obtained that suggested the entrance of leucocytes into these hyaline fibres. The sarcolemma nuclei were also increased, sometimes several fold. At one point in the muscle there was an exaggeration of nuclei, presenting the appearance of an abscess. Here the muscle fibres were most disintegrated, and many cells of the connective-tissue type were discernible. Adjacent to this the tissues contained very few normally staining nuclei, and the tissues were quite without stain and presented a finely granular or reticulated appearance, suggestive of fibrin. Such nuclear stain as was obtained here was taken by fragments of nuclei, and these presented the greatest variety of form, being small, point-like, drawn out, and usually distorted, but agreeing in the common property of staining intensely with fuchsin. This is the area of most profound activity of the irritant. The fragmented nuclei in this situation came from two sources: the fixed cells and the emigrated cells or leucocytes. Just at the edge of the tumor where the necrotic tissue passed into the more nearly normal tissue, the participation of the fixed cells in the process of nuclear fragmentation was more readily seen. As the deeper parts of the tissue were reached the extensive nuclear fragmentation grew less and less, but here and there were small and larger areas of cells with round nuclei. These were sometimes only three or four in number, while again they were more numerous. They were the fixed cells. Leucocytes were not always found in these areas; they were often absent from the smaller, but were usually present in the larger. The small round cells, as stated, were regarded as derived from the fixed cells; and while they were most frequently not associated

FIG. 1.



A. C. ABBOTT, *del.*

with cells which had fragmented nuclei, yet occasionally the reverse was the case.

The lymphatics in this locality contained an increased number of leucocytes. Moreover, the endothelial cells lining their walls were sometimes necrotic and contained fragmented nuclei. In a section of a lymphatic, for example, in which several elongated endothelial cells were seen, perhaps one-half showed a distinct fragmentation of their nuclei. The smaller veins, also, as before mentioned, were often almost full of leucocytes, and in these too, at times, the endothelial cells of the intima had suffered this form of cell necrosis.

The further removed the tissues were from the point of most intense action of the irritant the less the alteration in their structure; but even in the most peripheral portion of the tumor mass there was cell death, as indicated by the fragments of nuclei in the tissues. A single nuclear figure was found in the fixed cells about the middle of the specimen, in a place where there was apparently active proliferation of the fixed cells.

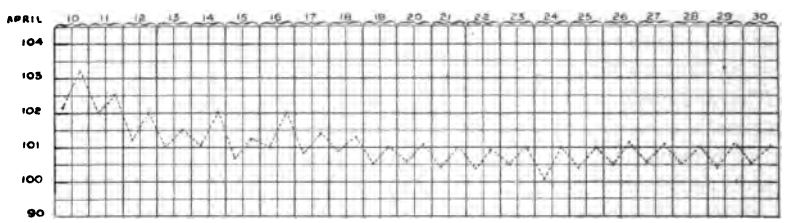
The specimen stained by Weigert's fibrin method showed a focus containing many leucocytes and clumps of diphtheria bacilli. This corresponds with the abscess like area above described.

The conspicuous alteration in the tissues generally at this point was the changes in the nuclei of the fixed and wandering cells, a nuclear fragmentation in all respects identical to that described by Oertel (2) in the tissues of the human subject dead of diphtheria, and by Welch and Flexner (3) in the tissues of animals that have succumbed to the experimental form of the disease. Under a low magnifying power this condition is seen as islands of irregular granules that stain intensely with the ordinary nuclear dyes and lie scattered through a tissue that either does not stain at all or very imperfectly. In addition to these granular areas, that could readily be seen to consist of nuclear detritus, were other irregular masses that stained also with the basic aniline dyes, but which were much less coarsely granular than the groups of nuclear fragments. Under a higher magnifying power these latter resolved themselves into masses of bacilli in all morphological and staining respects identical with the bacillus diphtheriæ, except that in most instances the irregularity of outline and staining peculiarity was more marked than common. (See Plate: Fig. 1.)

In certain sections these groups of bacilli appeared as irregular rosette-like patches of varying size, while again in sections made from a different portion of the tumor, or running in another direction; they appeared as irregular, broken, granular lines. The tissue about them was in all cases nearly completely destroyed (see Plate), so that it was impossible to make out definitely the relation of the organisms to the surrounding tissue; but as a result of examination of a number of sections, it is probable that they had developed in and filled lymphatic spaces. In the irregular, roundish or rosette-like patches of bacilli the staining was sometimes less intense at the centre than at the margin of the clump, while in the long, irregular linear masses the color was more homogeneous. None of these masses of bacilli could be detected in the peripheral zone.

Cow No. 2. *Inoculated April* 10, 1893; *killed May* 1, 1893.—On April 10, 1893, at 10.30 A.M., Cow No. 2 was inoculated. She was thin but otherwise healthy; was suckling a calf at the time of inoculation. Prior to inoculation her temperature range had been from 100° to 103° F.; there was no eruption upon the udder nor was there anything to indicate a condition other than normal. She was inoculated in the soft tissues of the right shoulder with 1 c.c. of a bouillon culture of bacillus diphtheriæ, the virulence of which was at the same time tested upon a guinea-pig. The guinea-pig died in about sixty hours after having been inoculated with 0.5 c.c. of the same bouillon culture; the autopsy revealed the conditions commonly seen under these circumstances. The culture employed was about forty-two hours old and was but a few generations removed from a case of genuine, primary diphtheria.

TEMPERATURE CHART 2.



Cow No. 2. Inoculated with bacillus diphtheriæ April 10, 1893; killed May 1, 1893.

At the time of inoculation the temperature of the cow was 102.1° F.; on the evening of that day it went up 1.1° F., and fell a degree on the following morning. This was the highest rise of temperature after inoculation, as can be seen by the accompanying chart. She evinced no constitutional effects of the treatment, other than that she showed signs of weakness after the fifth day; and though careful watch was kept for an eruption upon the udder similar to that described by Klein, nothing of the kind appeared. For a few days after inoculation there was some swelling and considerable tenderness about the seat of operation, but after about seven or eight days the tenderness had apparently disappeared, and the swelling was gradually diminishing in size. This continued until the twentieth day after inoculation, when she was killed. At autopsy the following conditions were observed:

At the seat of inoculation there was a small subcutaneous nodule firmly adherent to the overlying skin, and freely movable over the underlying tissues. Viewed from the external surface this nodule was about 3 cm. in diameter, but when dissected out was not over 1 x 2 x 2.5 cm. in volume. It was *very* hard; upon section it was laminated, and tolerably sharply circumscribed; it did not fade away into the surrounding tissues. At one side of it the neighboring tissues were marked by minute hemorrhages.

The axillary and cervical lymphatics were not enlarged, nor were any of the other subcutaneous lymphatic glands. The lungs were normal, containing no hardened areas, nor any spots indicative of either a recent or a remote diseased condition. The parietal pleura was smooth and normal. The pericardium contained about 50 c.c. of clear fluid; both the pericardium and the endocardium were free from hemorrhagic points; no fluid in either the pleural or peritoneal cavities. On the lower surface of the left lobe of the liver, which was otherwise apparently normal, were grouped together three irregular yellowish spots, which extended a short distance into the substance of the organ. The smallest of these spots was about 1 cm. in diameter, and the other two were about 1 x 2.5 cm. in area. Beyond a few scattered irregular whitish points, there were no other markings upon the liver.

The adrenal bodies were apparently normal. On the surface of the left kidney there was at one point a small whitish area, evidently due to fatty change, besides two or three minute cysts; the kidneys were otherwise normal. The spleen was normal. The other viscera showed no change. There was no change either upon the surface of the udder or in its substance, as was seen by parallel sections through the organ made at about one inch apart. From the centre of the tumor mass, at the seat of inoculation, five blood-serum slants were inoculated; after ninety-six hours at 37° C., they all remained sterile.

Microscopic examination of the seat of inoculation revealed a condition that was in general identical with that described in the same locality in Cow No. 1, but differed from it in certain details. The process, while everywhere conspicuous for cell death, as evidenced by fragmentation of the nuclei, was, nevertheless, not so far advanced as in Cow No. 1. In many of the lymphatic spaces between the tissue bundles masses of leucocytes could be made out, some of which had undergone complete necrosis, while others were less affected. Throughout many of these masses of leucocytes bacilli were scattered about in an irregular way, and in some instances small clumps of from four to six bacilli could be seen, having the appearance of being located within the bodies of leucocytes. In none of the sections could the tangled clumps of long, irregular bacilli, as seen in Cow No. 1, be detected, but where the organisms were found they were always scattered about irregularly, as described above. Where muscle fibres were present they were in an advanced condition of hyaline degeneration, and were frequently to be seen penetrated by leucocytes. Though bacilli in all morphological and staining respects identical with the bacillus diphtheriæ were present in large numbers, it was nevertheless impossible to obtain cultures of them from scrapings from the centre of the tumor. As stated, five blood serum tubes were inoculated, but in none of them did the organisms develop. The yellowish points that were found by macroscopic examination of the lower surface of the left lobe of the liver, were found microscopically to extend some distance into the substance of the organ, and to represent areas of fatty metamorphosis.

Bacteriological Examination of the Milk.

The point upon which special stress is laid in the experiments of Klein, is the discovery of the bacillus diphtheriæ in the milk of the cows that he had inoculated. For this reason particular care was taken with this portion of our work.

The investigation of the milk of Cow No. 1 began on the day of inoculation and continued every day for the four succeeding days, when a day was skipped; then two days were missed, after which the samples were collected at somewhat longer intervals. The teats were washed clean and the sample of milk for study was collected only after milking had been in progress for a short time. The milk was received in sterilized test-tubes provided with sterilized cotton plugs, and the bacteriological study began in, at most, ten minutes after it was collected.

In the majority of cases the blood-serum mixture of Löffler was employed in these analyses, but in a few instances slanted glycerin-agar and Petri plates of glycerin-agar were substituted. For each inoculation approximately $\frac{1}{20}$ c.c. of the milk was used. The results of the bacteriological study of the milk on nine different days succeeding the inoculation were negative in all cases, in so far as the presence of the bacillus diphtheriæ was concerned, and in general the tubes and plates contained fewer organisms of any character than one would have anticipated.

The results of these studies in detail are as follows:

November 8, 1892. One-half hour after inoculation about $\frac{1}{20}$ c.c. of milk was smeared upon the surface of each of three slanted glycerin-agar tubes; from each of these a blood-serum (Löffler's) slant was inoculated. At 37° C. no colonies of bacillus diphtheriæ developed. This milk was placed at 37° C. for twenty-four hours, and again two blood-serum slants were inoculated, but no colonies of the Löffler bacillus appeared. Similar results were obtained with a set of glycerin-agar Petri plates.

9*th*. Two samples of milk were examined—one at the beginning and the other at the end of the milking. From each sample two smears upon slanted blood serum, and one set of glycerin-agar Petri plates were made, but no colonies of bacillus diphtheriæ appeared. Both samples of milk were then placed at 37° C. for twenty-four hours, after which two blood-serum tubes were inoculated and one set of glycerin-agar plates were made from each of them, but still no colonies of Löffler's bacillus developed.

10*th*. Again samples were collected from the beginning and end of the milking. From each sample two blood-serum slants and two sets of glycerin-agar plates were prepared. No colonies of the bacillus diphtheriæ appeared.

11*th*. From samples taken at the beginning and at the end of the milking two blood-serum slants and one set of glycerin-agar plates were prepared. All failed to reveal the presence of colonies of bacillus diphtheriæ.

12*th*. Two blood-serum slants were prepared from the milk at the beginning and two from a sample from the end of the milking. No colonies of bacillus diphtheriæ developed.

At this date the samples from November 9th and 10th, that had been standing at the room temperature since they were collected, were examined by means of the blood-serum slants, but no diphtheria bacilli could be found.

14*th*. Two blood-serum slants and one set of glycerin-agar plates were made from a sample of milk collected a short time after milking had been in progress. No colonies of bacillus diphtheriæ appeared.

17*th*. Two blood-serum slants were prepared from the milk at the beginning, and two similar tubes from that at the end of the milking. Both negative as regards bacillus diphtheriæ.

December 3. Four blood-serum slants, each prepared with about $\frac{1}{10}$ c.c. of milk of this date, did not reveal the presence of any colonies of bacillus diphtheriæ.

10*th*. No diphtheria bacilli could be detected in the milk of this date, though three samples from different teats were examined upon three sets of glycerin-agar plates.

In the course of these examinations all bacilli that might, by any possibility, have been mistaken for the bacillus diphtheriæ were isolated in pure culture and their biological peculiarities studied. In no case were any of them identical in their cultural peculiarities with the bacillus of Löffler. Seven different species that were isolated were inoculated subcutaneously into guinea-pigs. None of them possessed any pathogenic properties for these animals.

Of these seven species, three were at times a little like the bacillus diphtheriæ in their morphology; that is to say, irregular, curved, clubbed, and segmented forms that stained irregularly, could be seen upon microscopic examination. In some of their cultural peculiarities they had also certain points suggestive of Löffler's bacillus, but when all of their biological properties, and particularly their pathogenic powers were tested, it was easy to see that they bore no relation whatever to this organism.

The bacteriological studies of the milk of Cow No. 2 were made upon six different days prior to inoculation and upon nine days succeeding. The object in making these studies before the animal was subjected to the experiment, was to determine if there were any organism or organisms present in the milk that might be confounded with the bacillus diphtheriæ. Two or three organisms having irregularities in their morphological and staining peculiarities were detected,

but their behavior under different methods of cultivation readily demonstrated that they were not to be mistaken for the Klebs-Löffler bacillus.

The studies upon the milk, which, as stated, covered nine days succeeding the inoculation, were negative in so far as finding the bacilli that had been injected into the tissues of the animal is concerned. As in the studies made before inoculation, there appeared, occasionally, bacilli which in morphology alone were a little suggestive of the bacillus diphtheriæ, but which could easily be differentiated from it by culture tests.

Another interesting point in connection with these analyses is the unexpectedly small number of organisms of any kind that appeared in the milk. The teats were not disinfected or washed, but the samples of milk, collected by myself, were taken only after I had been milking for a short time. They were, as usual, collected in sterilized test-tubes.

The details of these analyses are as follows:

Examination of the Milk before the Cow was Inoculated.

March 29, 1893. Three blood-serum tubes were each smeared with three loopfuls of the milk. After forty-eight hours at 37° C., two of the tubes were still sterile, the third contained a few colonies of cocci.

31*st*. Two blood-serum tubes were each smeared with three loopfuls and one with five loopfuls of milk. Of the tubes inoculated with three loopfuls of milk, one remained sterile; on the other there developed one colony of a coccus and one of a short bacillus, while on the remaining tube there appeared a single, small, dry colony of a minute bacillus.

In morphology alone this latter organism might, *at times*, pass for the bacillus diphtheriæ. But in this respect it varies, and by culture methods is easily seen to be of no relation to that organism.

April 1. Three blood-serum slants each inoculated with $\frac{3}{20}$ c.c. of the milk. After forty eight hours at 37° C., there appeared on one of the tubes a group of lemon-yellow colonies; on another an orange colony of cocci and three or four colonies of a straight bacillus; while the third tube remained sterile.

3*d*. Three blood-serum slants each inoculated with $\frac{3}{20}$ c.c. of the milk. After forty-eight hours at 37° C. one tube was sterile, another contained a single yellow or orange-colored colony, and the third had a diffuse white growth at the bottom consisting of a coccus.

5*th*. Four glycerin-agar plates made with 0.5 c.c., 0.4 c.c., 0.25 c.c., and 0.2 c.c. of the milk. After seventy-two hours there had developed three colonies, one colony, one colony, and four colonies on the plates in the order named. None of these organisms was in any way suspicious.

6th. Four Petri plates of glycerin-agar were made as follows: With 0.5 c.c., 0.5 c.c., 0.25 c.c., 0.25 c.c. of the milk. There developed respectively four, twenty-one, thirteen, and three colonies. They consist of small yellow colonies of cocci, colonies of large cocci, and a few of irregularly staining bacilli—the latter easily differentiated from bacillus diphtheriæ.

Bacteriological Examination of the Milk after Inoculation.

April 10, 1893. Ten minutes after injecting 1 c.c. of a bouillon culture of virulent bacillus diphtheriæ into tissues of right shoulder, two blood-serum slants were each inoculated with $\frac{3}{10}$ c.c. of the milk. On one tube fourteen colonies developed, a portion of which were lemon-yellow and a few orange in color. On the second tube seven colonies similar to those on the first tube developed. Nothing to suggest bacillus diphtheriæ.

11th. Two samples of milk—one at beginning the other near the end of the milking.

Beginning sample. Two blood-serum slants inoculated with 0.2 c.c. of milk. On one tube there developed thirteen colonies; on the other, no colonies, but there were found a few lancet-shaped bacilli in the fluid at the bottom of the tube, after forty-eight hours at 37° C.

Sample at end of milking. Two blood-serum slants each inoculated with 0.2 c.c. of the milk. On one there developed eleven colonies; the second was still sterile after forty-eight hours at 37° C. No diphtheria bacilli appeared on the tubes from either sample.

12th. Four blood-serum slants each inoculated with 0.2 c.c of the milk. After forty-eight hours at 37° C., there developed five colonies, two colonies, and thirteen colonies on three tubes respectively, while the fourth remained sterile. No diphtheria bacilli.

13th. Four blood-serum slants each inoculated with 0.2 c.c. of the milk; two of them at beginning and two at end of milking. On the former two there developed two colonies and one colony respectively, and on the latter two, one colony and no colonies after forty-eight hours at 37° C. No diphtheria bacilli.

14th. Sample of milk at beginning and another at end of milking:

From former, each of three slants, two blood-serum and one glycerin-agar, were inoculated with 0.2 c.c. of the milk. Both blood-serum tubes remained sterile and one colony developed upon the glycerin-agar tube. The three slants, one blood-serum and two glycerin-agar, each inoculated with 0.2 c.c. of the milk from the end of the milking, resulted as follows: On the blood-serum tube one colony of a coccus, on one glycerin-agar slant twenty-four colonies of a white coccus, and on the other twenty-eight colonies of apparently the same organism. No diphtheria bacilli were found.

15th. Six glycerin-agar slants were each inoculated with 0.2 c.c. of the milk at beginning of milking. After forty-eight hours at 37° C., there developed two, three, seven, five, two, and three colonies respectively. None of them were bacillus diphtheriæ.

Six glycerin-agar slants were each inoculated with a similar amount of the milk from end of milking. There developed seventy, fifty-two, fifty-eight, fifty-six, forty-eight, and forty-eight colonies respectively, the majority of which are of a lemon-yellow color, a few are quite white, and two are salmon-color. There are no colonies that could in any way be mistaken for those of the bacillus diphtheriæ.

17*th*. Eight glycerin agar slants inoculated with 0.2 c.c. each—four from sample at beginning, and four from sample at the end of milking. After forty-eight hours the former four showed no colonies; of the latter four, three remained sterile, and two colonies appeared on the remaining tube. Neither of them were bacillus diphtheriæ.

18*th*. A sample of milk at beginning of milking and one at end of milking, examined.

Eight glycerin-agar slants each inoculated with 0.2 c.c. of milk—four from first and four from second sample.

After forty-eight hours at 37° C., there developed on tubes from first sample, two, two, one, and one colony respectively. From second sample there developed twenty-three, seventeen, ten, and seven colonies respectively; all cocci. No diphtheria bacilli on any of the tubes.

20*th*. Two samples of milk examined:

Sample 1. Two blood-serum and two glycerin-agar slants each inoculated with 0.2 c.c. of the milk. There developed after forty-eight hours at 37° C., twelve, twenty-six, none, and no colonies respectively.

Sample 2. Two blood-serum and two glycerin-agar slants inoculated with 0.2 c.c. of the milk. Results after forty-eight hours at 37° C., twelve, none, one, and no colonies respectively. No diphtheria bacilli on tubes from either sample.

Though it is possible for a few scattered diphtheria bacilli to have been present in the milk and escaped efforts to detect them, I nevertheless think the above protocol speaks for a fair trial in this direction.

Though the bacillus diphtheriæ was not found in the milk of either of the two cows experimented upon, I should not have been very much surprised had it appeared; for it has recently been demonstrated by Ghriskey and myself, working together, (4) that in exceptional instances diphtheria bacilli when deposited under the skin of smaller animals (guinea-pigs) may be found in the lymphatic apparatus of the omentum, and that when the injections are made into the testicles of these animals they were also found in masses in the omental lymph spaces of three out of four animals inoculated. In all these experiments there was strong evidence in favor of many, if not all of them, having been conveyed from the seat of inoculation, either

in the loose subcutaneous tissues or the tissues of the testicle, to the points in the omentum at which they were found, through the phagocytic activity of the wandering blood-corpuscles, the leucocytes.

Morphological Variations of the Bacillus Diphtheriæ.

One of the points upon which Klein lays particular emphasis is the presence in the degenerated muscle fibres, at the seat of inoculation in one of his cases, of long threads in tangled clumps. He refers to them in the following terms (*loc. cit.*, p. 173):

"Microscopic examination of the masses of bacilli in the necrotic portions of the tumor, as also of those implicating the muscle fibres, revealed the following remarkable fact, namely, that many bacilli had become threads, some of considerable length, and containing granules in their course, characterized by intermediate or terminal buds or swellings, spherical, oval, or flask-shaped. In a word, the organisms had taken on forms which are but exaggerations of what had been before observed in cultures of this bacillus. I draw particular attention to the bacilli cultivated from the milk of Cow No. 2, where some of the threads were seen to be possessed of terminal flask-shaped enlargements, reminding one vividly of the growing and germinating hyphæ of a mycelial fungus."

We have searched carefully the sections through the seat of inoculation of both of our cows, but have failed to find this remarkable appearance described by Klein. In the first cow clumps of rather long, irregularly staining and beaded bacilli were easily to be seen in the necrotic areas, while in the second cow the organisms were not arranged in clumps, were smaller, and were scattered, as stated, through masses of leucocytes lodged in the connective-tissue lymph spaces.

We have not felt called upon to consider the long, irregular forms seen in the tissue from the first cow as remarkable, for similar forms of this organism are practically constant when it is cultivated upon Löffler's blood-serum mixture. We have made a series of studies upon the variations in the morphology of this organism, and find that its form changes markedly under certain different conditions of environment. That is to say, its morphology is always more regular and smaller on glycerin agar-agar than on any of the other media used for its cultivation; while upon Löffler's blood serum the other extremes of development appear; here one sees (instead of the very

short, spindle, lancet, club-shaped, always segmented and regularly staining forms as seen upon glycerin-agar) long, irregularly staining threads, that are sometimes clubbed and sometimes pointed at their extremities. They are usually marked by areas that stain more intensely than do the rest of the rod, and at times they may be a little swollen at the centre. These differences are so conspicuous that microscopic preparations from cultures of the bacillus diphtheriæ upon glycerin agar-agar and blood serum when placed side by side, would hardly be considered as of the same organism, unless its peculiar behavior under these circumstances was already known.

We have endeavored to discover the cause of this variation, and for this purpose have studied the growth of the organism upon a number of different media, with very interesting but not entirely satisfactory results. On plain nutrient agar-agar (that is, nutrient agar-agar without glycerin); on solidified egg-albumen; on a medium that we are now using consisting of dried albumin, as found in commerce, dissolved in bouillon (about 10 grammes albumin to 100 c.c. of bouillon containing 1 per cent. of grape-sugar); in bouillon without glycerin and in bouillon to which a bit of hard-boiled egg has been added, the morphology of the organism is about intermediate in both size and outline between the forms seen upon glycerin agar-agar and Löffler's blood serum. There will appear about an equal number of short segmented and long irregularly staining forms, but in general the longest are rarely as long as the long forms seen on blood serum, and throughout they are not so conspicuous for the irregularity of their staining.

In cultures made upon two sets of nutrient agar-agar tubes differing only in the fact that one set contains glycerin to the extent of 6 per cent., while the others contain none, a noticeable difference in morphology can usually be made out; while the forms on the glycerin-agar cultures are throughout small, pretty regular in size, shape, and staining, those on the plain agar are larger, stain more regularly, vary more in shape, and when stained by Löffler's blue are not so uniformly marked by the pale transverse lines that give to them the appearance of being made up of numerous short segments.

This observation, in connection with what has already been said, might lead to the suspicion that the small amount of glycerin present was instrumental in bringing about these conspicuous differences. To

FIG. 2.

FIG. 3.

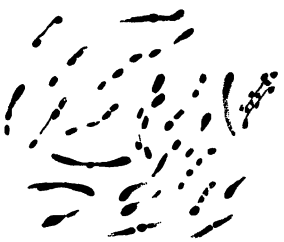


FIG. 4.

A. C. ABBOTT, *del.*

determine if this is the case, Löffler's blood serum was prepared containing 6 per cent., 10 per cent., and 20 per cent. of glycerin, but cultures upon it were in no way identical with those found upon agar-agar containing 6 per cent. of glycerin. The morphology of the organisms that grew differed from that seen upon Löffler's serum without glycerin only in being a trifle shorter and more markedly beaded. The protoplasmic portions that took up the staining were often perfectly round and extended a little beyond the lateral margin of the rod in which they were located. Many of these beads were almost black in color; indeed, these cultures were conspicuous for the number of these blackish points, even after only twenty-four hours in the incubation. No growths appeared upon the tubes containing 20 per cent. of glycerin. The effect of pure glycerin was tested upon long forms that had already developed upon Löffler's serum for twenty-four hours, by scraping the growth from the surface and mixing it with pure glycerin, but after twenty-four hours of this treatment the morphology of the long, irregularly staining rods was not altered.

In Figs. 2 and 3 we have endeavored to depict the appearances of this organism as obtained from glycerin-agar and from Löffler's blood serum, and, as can be seen, the difference is marked.

Fig. 2 represents the appearance of the organism as obtained from a glycerin-agar culture twenty-four hours old, while Fig. 3 is the same organism from a blood-serum culture of the same age.

It is particularly interesting to note the sudden transition that occurs in the morphology of this organism when placed upon blood serum after it has been cultivated upon glycerin-agar through a number of generations, and *vice versa*. We have repeatedly isolated it upon glycerin-agar from single colonies directly from the throat of a diphtheritic patient or the seat of inoculation of an animal dead of the experimental form of the disease, and continued its cultivation upon this medium for six or eight generations, in all of which practically none but the short segmented varieties could be seen, but with the first generation that appeared, when now transferred to Löffler's blood serum, the tendency throughout was to the formation of the long, irregular threads diagrammatically represented in Fig. 3. The reverse is true when it is carried along for a time on serum and then transferred to glycerin-agar.

We have made these observations on five cultures from undoubted cases of primary diphtheria, upon cultures from two cases of membranous rhinitis, and upon one culture of the so-called pseudo-diphtheritic bacillus, and find no deviation in the behavior of any of them from what has been said.

It is impossible to say what it is that causes these differences, and with the evidence at our disposal it is, perhaps, premature to offer an hypothesis, but certainly it appears that the blood serum offers something that is particularly conducive to the growth of the outer envelope of the bacilli, and that this portion of the cell grows more rapidly than do its protoplasmic contents, causing in this way breaks in the continuity of the cell protoplasm as seen in stained preparations. (Figs. 3 and 4.) Whether this is true or not, there is apparently a difference in constitution between the portions of the cell, as cultivated upon blood serum, that take up staining, and that portion that is seen as either a colorless or only faintly stained sheath or tube. These differences can readily be brought out by micro-chemical means; for example, if one prepares a cover-slip from a fresh (twenty-four hours old) serum culture of the bacillus diphtheriæ, and stains it for a few minutes in saturated watery solution of Bismarck-brown, and subsequently by Gram's method, that portion of the cell that is usually colorless, or nearly so, is now seen to be brown, while the protoplasmic contents will be of an intense violet color. Fig. 4 represents a preparation made from a blood-serum culture by this method.

From what has been said it is easy to conceive that one accustomed to study this organism upon agar-agar or gelatin would hardly be prepared for the striking alteration that it undergoes in its appearance when under more favorable conditions of growth, and for this reason it is important to recognize the necessity of an acquaintance with the growth of the organism under the different conditions of environment.

Long, irregularly staining, clubbed, and curved forms similar to those that are constantly seen upon Löffler's blood serum, even after only twenty-four hours at the temperature of the incubator, are often referred to collectively as involution or degenerate forms of this organism; but from these studies I feel justified in questioning the accuracy of this view; at all events it is difficult to reconcile the

voluminous growth of this organism, as seen upon blood serum after twenty-four hours, with the opinion that the organisms of which it is composed are in a condition of degeneration.

SUMMARY.—The results of our experiments have differed from those of Klein in several essential points. We have failed to obtain cultures from the seat of inoculation of either of our cows at autopsy. In one case the animal died sixteen days after inoculation, and in the other she was killed on the twentieth day after the experiment was begun. In both cases microscopic examination of the tissues revealed the presence of the bacillus diphtheriæ in relatively large numbers.

In neither of the two cows operated upon by us did an eruption appear upon the udder or teats. Careful watch was kept, but at no time during the experiments could anything abnormal be detected upon this organ.

We have subjected the milk from both cows to careful and prolonged study, and have failed in both instances to detect the bacillus diphtheriæ in it.

The pathological appearances in the internal organs noted by Klein were not looked for in Cow No. 1, for the reason given; but in Cow No. 2 there was no trace of disease of any character in either the lungs, pleuræ, or serous surfaces of the heart.

From the description of the seat of inoculation in the cows experimented upon by Klein, we cannot say whether the pathological lesions found by us were similar to those obtained by him or not. In neither cow have we found at the seat of inoculation bacilli sufficiently peculiar in their morphology to justify us in likening them to the germinating hyphæ of mycelial fungi; but we did find in Cow No. 1 bacilli the morphology of which was strikingly like the long irregular forms of this organism that predominate when it is grown upon Löffler's blood-serum mixture. In Cow No. 2 the majority of the bacilli were short and irregular in outline, presenting nothing peculiar in their appearance.

NOTE.—Before closing, I wish to express my indebtedness to Dr. Simon Flexner, Associate in Pathology, Johns Hopkins University and Hospital, for his kindly assistance in my studies of the pathological lesions found in these experiments; and to Professor Pearson

and Dr. Turnbull, of the Department of Veterinary Medicine of the University of Pennsylvania, for their valuable aid during the time that the cows were under observation in this institution.

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3. *Welch and Flexner:* The Histological Changes in Experimental Diphtheria. Johns Hopkins Hospital Bulletin, August, 1891, No. 15.

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DESCRIPTION OF PLATES.

FIG. 1.—Area of necrosis at seat of inoculation of Cow No. 1, showing the condition of fragmentation of the cell nuclei and clumps of irregularly staining bacillus diphtheriæ. Stained with Bismarck-brown and Gram's method. Leitz oil immersion $\frac{1}{12}$, ocular 4, tube 160 mm.

FIG. 2.—Bacillus diphtheriæ, second generation on glycerin agar-agar, after twenty-four hours at 37° C. Stained with Löffler's blue. × about 1500 diam.

FIG. 3.—Bacillus diphtheriæ after twenty-four hours at 37° C. on Löffler's blood-serum mixture. Stained with Löffler's blue. × about 1500 diam.

FIG. 4.—Bacillus diphtheriæ after twenty-four hours at 37° C. on Löffler's blood-serum mixture. Stained with Bismarck-brown and Gram's method. × about 1500 diam.

GONORRHŒAL MYOCARDITIS.

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In spite of the fact that gonorrhœa is one of the most common diseases, our knowledge of the pathological lesions is obscure. This is due to the fact that the disease is not open to experimental investigation and acute cases rarely come to autopsy. We know but little of the exact character of the lesions in the mucous membrane of the urethra, and the secondary lesions are still more obscure. It will not be worth while to go over the general literature with regard to the part which the organisms described by Neisser in 1881 play in the process. Since Neisser's description of the organism our knowledge concerning it can be briefly stated as follows: It is agreed by all, or nearly all, who have studied the disease, that the gonococcus is found in the discharge from the urethra in all cases of acute gonorrhœa. The organism is characterized by morphological, staining, and cultural properties. It is easily recognized, being stained by most of the aniline colors. It is a micrococcus, and is always found in pairs or in tetrads. The single organisms are not perfectly round, but have more or less of a biscuit shape, the adjoining sides of each pair being flattened. It often presents a rather peculiar appearance in the pus-cells, being crowded in one side of the cell and pushing the nucleus before it. The nucleus of the cell is never invaded. Unlike all of the pus organisms, it is decolorized by the solution of iodine used with the Gram stain. It also differs from the pus organisms in its cultural properties. It will not grow on the ordinary culture media, and so far it has only been possible to cultivate it on solidified human blood serum or on a mixture of this with agar-agar.

The organism has only been cultivated by a few observers, and its cultivation is apparently attended with great difficulties. The first

successful cultivation and the first exact study of the inflammations caused by inoculating the organism were made by Bumm. Bumm succeeded in growing it on human blood serum which he obtained from placentas. His studies of its pathogenesis were made on the conjunctiva, where he succeeded in producing a typical gonorrhœal inflammation by inoculating the mucous membrane with pure cultures of the fourth and fifth generations. According to Bumm, the action of the organism is essentially superficial; he found that when the conjunctiva was inoculated with a pure culture of the organism the first action was to produce an increase in the conjunctival secretion, then the organism entered into the superficial layers of the epithelium. They were generally found between the epithelial cells and occasionally in the papillary bodies. On the second day after the inoculation there was a marked emigration of leucocytes from the vessels beneath. Some of the leucocytes entered into the epithelium along with the cocci, pressing aside the cellular elements. When the epithelium is destroyed a layer of fibrino-purulent exudation is found which contains masses of the organisms. The organisms do not enter into the connective-tissue. Bumm found that the epithelium of the cornea is not invaded by the organism, which appears only to exert its action on cylindrical epithelium or on epithelium closely related to this. Bumm found that the gonococcus does not grow in the mucous membrane of the vagina, and gonorrhœa in the female is an affection either of the urethra or of the cervix uteri.

Bokhardt claims to have cultivated the organism, and studied the result of its inoculation into the urethra. He injected into the healthy urethra of a man forty-five years old what he supposed was a pure culture of the gonococci, and obtained a characteristic discharge with a secretion containing a number of the organisms. The man was affected with an incurable nervous disorder. He died ten days after the injection from a hypostatic pneumonia. At the autopsy an intense acute inflammation of the urethra, of the bladder, and of the pelvis of the kidney was found. In the sections made of the tissues Bokhardt obtained the organisms. No one on carefully reading the article of Bokhardt's can fail to be convinced that the disease which he produced in the man was not gonorrhœa, but a purulent infection. It is more than probable that the organisms in his culture were not gonococci but some one of the pus organisms. They were

grown on agar-agar, and all of the evidence which we have on the subject shows that the gonococci do not grow on this medium. Bokhardt's description of the pathological process in the urethra differs materially from that described by Bumm in the conjunctiva. Bokhardt obtained the organisms both from the epithelium and in the submucous tissue of the urethra. In the deeper tissues they were found chiefly in the lymphatics, which were often completely plugged with them. The illustrations which accompany the article of Bokhardt's show that the supposed organisms which he found in the deeper layers of the tissue were not gonococci or any other organisms, but probably the granular plasma cells.

Although the pathology of chronic gonorrhœa in the urethra and the lesions following this have been carefully worked out by Finger and others, we have not been able to find in the literature a single case, with the exception of the case of Bockhardt's which we have referred to, in which the lesions in acute gonorrhœal urethritis and the part which the gonococcus plays in their productions have been studied.

The secondary affections following gonorrhœa have been more carefully investigated. These secondary infections may be briefly stated to consist in purulent inflammation of the canals and passages, in both male and female, connected with the urethra or vagina, acute swelling of the inguinal glands, acute inflammation of the joints and synovial surfaces, and pericarditis. There are two theories with regard to the pathogenesis of the secondary infection. They have been considered by some to be the result of an extension of the gonorrhœal process and an infection of remote parts with gonococci; and by others to be the result of a mixed infection, and to be due to various organisms, especially the pus organisms which have entered into the tissues from the local lesions and been carried to the various secondary foci. Gonorrhœal rheumatism is the most common of the secondary affections following gonorrhœa, and a great deal has been written about it.

One of the most extensive articles on the subject is that of Loeb in the *Deutsches Arch. für klin. Med.* Different authors give different figures as to its frequency. Fournier, who has had the most extensive experience and the largest number of statistics, gives one case of joint affection to sixty-four of gonorrhœa. Besnier gives the relation

of 1 : 50, and Grissolle as 1 : 35. Loeb, without giving any definite figures, thinks that the affection is much more frequent than would appear from these figures. Some authors are disposed to deny any connection at all between the rheumatism and the gonorrhœa; others think that there must be an especial predisposition to rheumatism which is called into activity by the urethral affection. In most cases the rheumatism does not seem to be produced early in the disease. It frequently follows a torpid state of the gonorrhœa and rarely appears before from five to fourteen days. As a rule, most authors agree that the rheumatism is only seen when the gonorrhœal process attacks the posterior portion of the urethra. It is certainly much more frequent in men than in women. There seems to be a marked difference in the symptoms produced in gonorrhœal rheumatism as compared with those in the ordinary forms. Fever may be entirely absent in gonorrhœal arthritis, and even when it is present it has not the same long duration, and it may disappear while the affection of the joint obstinately continues. In some cases, however, there may be a considerable increase of the temperature in gonorrhœal rheumatism. Its duration is longer than the ordinary rheumatism. The number and situation of the joints differ in two cases. Generally speaking, in the gonorrhœal rheumatism fewer joints are affected than in the ordinary form. The knee-joint is one of those most frequently affected. The joints of the upper extremities are very frequently free. In Nolen's 118 cases the wrist-joint was affected 26 times, and in Fournier's 119 cases, only 14 times. There is a further difference between the two affections in the result of the treatment. The gonorrhœal joint affections do not yield to the treatment with salicylates as do the ordinary forms. In very few cases does the arthritis lead to suppuration and destruction of the joints.

Affections of the peri- and endocardium are also frequently seen as a complication of gonorrhœa. They are usually seen in combination with rheumatism, but they are by far less frequent in gonorrhœal rheumatism than in the other forms. Zeissl regards the comparative freedom of the peri- and endocardium from infections as characteristic of gonorrhœal rheumatism. Nolen found 15 cases in which the heart was affected in his 116 cases of gonorrhœal rheumatism, but it is probable that his figures are overdrawn. There are a number of cases reported clinically in which an affection of the peri- and endo-

cardium has been found in gonorrhœa. Traube makes repeated mention of heart affections in gonorrhœa.

With regard to the buboes, there need be no special reference. They are frequently found in gonorrhœa in both the male and female. The cultures made from the glands after removal are usually sterile.

In a number of cases organisms which have been considered to be gonococci have been found in association with these secondary lesions. Petrona claims to have found cocci in the joint affections which were similar to those found in the urethra, and he even found them in the blood in cases in which the joints were affected. Kramer also found gonococci in the joints. They were present in one of his cases, and in the other no organisms at all were found. Hahn has found cocci in gonorrhœal affections of the joints, but he does not regard them as true gonorrhœal organisms, but simply as pus organisms. He says that the organisms are only found in cases where the process in the joints is fresh and advancing rapidly. Where the process is more chronic they are not found. Haslund believes that the gonorrhœal rheumatism is due to a specific infection from the inflamed mucous membrane, but he was not able to find the gonococci in the joints. Leistikow investigated four cases of gonorrhœal arthritis, and found no organisms in the contents of the joints, nor in the blood of the patient. Hartley investigated a number of cases of gonorrhœal rheumatism in which he found typical cocci in the fluid. In a recent publication he inclines to the belief that the secondary affections are due to accidental infection with other organisms. With regard to the cardiac affections in gonorrhœa, they appear to be usually either cases of pericarditis or of endocarditis. Schaedler published a case of endocarditis ulcerosa which followed a gonorrhœal rheumatism, the rheumatism appearing three weeks after the beginning of the gonorrhœa. Eight months later symptoms on the part of the heart appeared which resulted fatally. Glusinski describes thirty-one cases in which complications on the part of the circulation were found in the course of gonorrhœa. All of his cases were clinical. He has recently reported a case of gonorrhœal endocarditis with extensive vegetations on the valves in which organisms similar to those in the accompanying urethritis were found.

The gonococci have been found by various authors in the buboes following gonorrhœa, in the peri- and para-urethral abscesses, and in

the various other local lesions. They have also been found in the tubes in cases of salpingitis following gonorrhœa. At present the belief is general that chronic salpingitis in the female is due to gonorrhœa. Organisms of the same general character as the gonococci have been found in the diseased tubes. So far as we can see from this brief review of the literature there are a number of varying opinions as to the pathogenesis of the secondary gonorrhœal affections, some believing that they are due to a specific infection with gonococci, while others believe that they are due to an accidental infection with other organisms which enter the tissues from the local lesions in the urethra.

The following case is of much interest, not only on account of the unusual character of the lesions but from the opportunity which was given for a close histological study of the acute process in the urethra and elsewhere. The case is from the Boston City Hospital in the service of Dr. Post, to whom I am indebted for the notes of the case.

W. H., admitted to the hospital September 30th. Urethral discharge first noticed four weeks before admission. Ten days after the gonorrhœa was first noticed the left knee began to swell, and became painful. This condition lasted three or four days, then extended to the right knee. Since the attack he has had pain and swelling in fingers, shoulders, ankles, etc. Cannot take long breath on account of pain in chest. On October 6th the pain in chest ceased, after having lasted since entrance. Pain in right knee persists. Temperature remains normal. October 7th he complained of much pain in chest. On examination there was a slight increase in cardiac dulness, but no murmur or pericardial rub. October 8th, pain in chest continued, and leeches were applied for its relief. October 9th, slept well, awoke at six, and took his milk. At seven cried out as in pain and fell out of bed. The house officer, who was summoned at once, found the patient gasping for breath, and no pulse perceptible at wrist. Patient died almost immediately after being seen by house officer. Temperature during the whole course of the attack did not exceed 99½°. The pulse kept under 110. The respirations were accelerated. The autopsy was made twenty-eight hours afterward.

The body was of medium size, slightly built, badly nourished. The general surface cyanotic. Both knee-joints, especially the right, enlarged, and gave clear fluctuation. The subcutaneous fat small in amount; muscles rather pale, somewhat diffusely stained with blood. The lungs somewhat stained with blood. The spleen slightly enlarged, both that and the liver free from adhesions. No adhesions in peritoneum. Peritoneal surface smooth everywhere. Diaphragm depressed on left side. Both lungs free from adhesions, and compressed by distended pericardium. The posterior and lower portions

of both lungs congested and œdematous. Mucous membrane of bronchi congested; vessels at root of lung free.

Pericardium enormously distended. The external surface congested, and covered with small hemorrhagic foci. In the pericardial cavity a large amount, about 800 c.c., of hemorrhagic exudation, in which there are large masses of clot. Both surfaces of peritoneum covered with thick membranous masses containing hemorrhages. The heart is firmly contracted. The aorta is very narrow. The myocardium of left ventricle is firm, and of a peculiar pale waxy color, somewhat resembling amyloid. Toward the endocardium, especially about the base of the papillary muscles, the tissue has a grayish, translucent, gelatinous appearance. This extends in places into the tissue of the myocardium for a considerable distance. It is especially marked toward the apex of the ventricle. In places this pallor and translucent appearance is associated with marked hæmorrhagic infiltration. This condition of the myocardium is almost confined to the left ventricle. There is some evidence of it on the right side, but it is not so well marked. On the anterior inner surface of the left auricle there is an area of 2 x 2½ cm. where the muscular tissue is substituted by a pale opaque tissue; the centre of this is soft and almost broken down.

The spleen is enlarged; the follicles prominent. Both liver and kidneys show slight acute swelling. All of the follicles of both large and small intestines are enlarged and hyperæmic. In the small intestines the follicles have the character of small polypi. The Peyer's patches are enlarged, but there is no ulceration. All of the mesenteric lymph glands are slightly enlarged. The right knee-joint is greatly distended. On section about 100 c.c. of gelatinous pus escapes. The pus is stringy and rather transparent. The muscles above the joint, in the immediate neighborhood, show some diffuse purulent infiltration. The synovial membrane of the joint is swollen and intensely congested. There are papillary fungoid projecting masses of granulation tissue extending into the joint, having somewhat the appearance of masses of tuberculous granulations. On section these projecting masses have a white opaque edge, and below this the tissue is gelatinous and œdematous. The left knee-joint contains a smaller amount of this material. The joint is somewhat altered, but not to the same extent as the right. There is no general glandular enlargement.

The entire mucous surface of the urethra appears to be thickened and softened. The peri-urethral tissue is thickened and dense. About 4 cm. from the meatus there is a slight ulceration on the surface, apparently only involving the mucous membrane. The mucous surface is covered with a slight purulent exudation. Pus can be squeezed from the seminal ducts. There is a purulent infiltration extending from here into the prostate. On each side of the prostate an extensive purulent infiltration of tissue, with softening, and on the left side a distinct abscess. The seminal vessels, testicle, and epididymis show no alteration.

Microscopic examination of the pericardial exudation showed hemorrhage,

large numbers of pus cells, and large epithelioid cells. No gonococci were found in this exudation. The examination of cover-slips made from the urethra and from the knee-joint showed the presence of gonococci. They were abundant in the urethra, but comparatively few were found in the joint. In both places the organisms were only in the pus cells, and appeared to be identical. It is to be regretted that at the time it was not possible to make cultures from the tissues. All of the tissues were hardened in alcohol and subsequently examined.

Microscopic examination of the urethra. Section of the gland shows no lesion of the epithelium. Here and there on the surface there are adhering pus cells, some of which contain the gonococci. There is a gradual transition of the epithelium of the glans into that of the modified cylindrical epithelium of the urethra. The epithelium of the urethra is composed of numerous layers, but the cells have more the character of the cylindrical epithelium. The pigmented layer disappears, and the papillæ become less prominent. Just within the urethra there is a deep crypt, with several papillary projections from its wall. Here and there over the surface of this the epithelium appears to be broken through, and there is an intense round-cell infiltration of the submucous tissue. There are very few pus cells mixed with the round-cell infiltration. The tissue immediately beneath the mucous membrane, along almost the entire length of the urethra, shows a round-cell infiltration which is more or less focal, and in some places more intense than in others. In the vessels of this tissue there are a comparatively small number of leucocytes, and in places emigration is apparently taking place. The plasma cells in the tissue are very numerous, and many of them appear strikingly like cells filled with micro-organisms. There is no basement membrane giving a sharp line of demarcation between the epithelium and the tissue beneath. In the epithelium there is a considerable number of polynuclear leucocytes among the epithelial cells. In places there are irregularities on the epithelial surface, and small depressions resulting from the softening and breaking down of the cells. Gonococci are found in relatively small numbers. They are in the epithelium, both between and in the cells, but the greater part of them are found in the pus cells on the surface of the epithelium and between the epithelial cells. None are found in the deepest layers of the epithelium, nor are they in any of the tissues outside of the epithelium. Nuclear figures are found in the epithelial cells in the lower layers corresponding to the place where the lesions of the surface are most marked. The gonococci were found both as masses, filling up the entire cells, and as single pairs. The mucous membrane throughout the urethra in all the sections appears to be softened and exfoliated, and in places the granulation tissue is directly continuous with the surface. The sub-epithelial crypts show about the same condition as the surface of the urethra. The mucous membrane in places is entirely absent, and the granulation tissue comes distinctly to the surface. The cells found in the granulation tissue are of the ordinary types—both ordinary granulation cells and those with larger nuclei. The gonococci are

always most abundant where the purulent infiltration of the mucous membrane is most intense. They were found in the crypts and in the pockets of Morgagni, but in general they were less numerous here than on the surface of the urethra. Deep down in the tissue there are no lesions whatever to be made out. On sections passing through the membranous portion of the urethra, near the prostate, cutting across the numerous ducts and crypts, the same condition was found as in the other portions of the urethra. In the prostatic ducts there was an intense purulent inflammation, but very few gonococci were found. The prostatic ducts showed a purulent infiltration of the wall and of the surrounding tissue. In many places the epithelium was entirely destroyed. This condition extended up into the prostate, and on one side of this the tissue was entirely broken down, resulting in the formation of an abscess. No gonococci or other organisms were found in the abscess. The only other organisms found in the urethra were a few short bacilli on the mucous surface, which apparently had nothing to do with the inflammation, and were only accidentally present.

Sections from the heart from various places were examined after being hardened in alcohol. There is everywhere an intense pericarditis. The pericardium is universally thickened and swollen. In some places it has a thickness of 2 or 3 mm. The surface is generally smooth, but in places there are well-marked papillary projections. There is some fibrin loosely adherent to the surface, but there is no definite fibrinous exudation. In the thickened pericardium there are numerous widely dilated bloodvessels with thin walls. It is probable that the blood found in the pericardial cavity came from the rupture of these vessels. The thickened tissue of the pericardium is loose, infiltrated with pus cells, and contains numerous large round cells, some of which inclose pus cells in their interior. There are various changes in the myocardium, which are more extensive close to the endocardium than elsewhere. In the least marked lesions in the myocardium there appears to be simply some infiltration, with pus cells along the connective tissue septa, which are thickened and swollen. In some places the lesions in the myocardium, although most intense near the endocardium, appear to extend from the pericardium, and can be traced directly to this. In all of the areas where the purulent infiltration is seen there are various degrees of degeneration of the muscular fibres. In the slightest degree of degeneration they appear to be slightly swollen, diffusely stained, their nuclei disappear, and they frequently contain vacuoles. There is every degree of change from this up to a total necrosis of the muscular fibres, and an entire substitution of areas of purulent infiltration and necrosis for the normal tissue of the heart. There is little or no formation of granulation tissue. Some of the areas where the degeneration is most extensive involve almost the entire thickness of the ventricle extending up to the pericardium. In such places there are large areas of necrotic tissue, with purulent infiltration extending widely into the tissue beyond the necrosis. The most pronounced lesion is found in the left auricle. In this there is a very large area of necrosis and suppuration, which

involves the entire thickness of the wall. Extensive hemorrhage was found in some of the necrotic foci. This was most extensive in the auricle. The gonococci are found in the sections in considerable numbers. They were most numerous in the most acute focus in the auricle. They were found also in the ventricle, but in much smaller numbers. In the pericardium very few were found. In the left auricle they were present in some of the sections in enormous numbers. In places almost every pus cell contained them. None were found in the tissue outside of the cells.

Sections of both knee-joints were examined after the tissue was hardened in alcohol. On the surface, corresponding to the opaque appearance noticed at the autopsy, there is an area of purulent infiltration extending only a short distance into the tissue, not more than 1 mm. In this tissue the vessels were dilated and tortuous, and frequently contained numerous pus cells. In the tissue beneath there are comparatively few pus cells. Most of the cells here are large and swollen, conforming to the general type of the epithelioid cells, and frequently containing large vacuoles within them. The surface of the joint is generally smooth, but in places it shows small depressions. The gonococci were found in but comparatively small numbers. They were never found deep down in the tissue, but were always either immediately on the surface or in the most superficial layers. They are most numerous where there are slight depressions and where the inflammatory process appears to be most intense. They were only found in the cells, and in their general character they agree with those found in the urethra.

When we look over this case we see that we have an acute gonorrhœa associated with remote lesions. These lesions appeared some time after the beginning of the attack of gonorrhœa, and in their general character they do not correspond with the lesions produced by the pus organisms. The process in the pericardium is not at all similar to any of the forms of peri- or myocarditis which are produced by other organisms. The most striking feature is the absence of any fibrinous exudation. The process consists in the production of various degenerations of tissue and necrosis with purulent infiltration, and a more or less extensive reaction on the part of the tissue shown in the formation of granulation tissue. In the knee-joint, also, the process is a peculiar one. There is a comparatively slight extent of distinct purulent infiltration, but the main thing is a formation of granulation tissue with mucoid degeneration of the cells. The presence of this mucus coming from the cells gives to the purulent accumulation in the joint its viscid and gelatinous character. Our conception of the process in the urethra agrees almost exactly with that of the study which Bumm made on the conjunctiva. The process, as far as the bacteria

are concerned, is a distinctly superficial one. There is more or less loss of the epithelium with purulent infiltration. In the surrounding connective tissue there is an extensive formation of granulation tissue. No gonococci were found in the depths of the tissue.

As we have said in the beginning, there are two opinions regarding the secondary lesions in gonorrhœa. One that they are due to a mixed infection, probably to other organisms than the gonococci entering the system from the lesions in the urethra; the other, that they are due to a direct metastasis of the gonococci. From the examination of this case, I think there is but little doubt that the secondary lesions were produced by the gonococci, the same organism found in the urethra. Unfortunately, the case is not a complete one, owing to the absence of cultures at the time of the autopsy. The organisms were only studied on the cover-slip preparations and in sections. The sections show apparently the same organisms in the tissues as were found in the mucous membrane of the urethra. It is not possible to absolutely distinguish the gonococci from the pus organisms by their morphology alone. Streptococci are often found in pus-cells arranged in pairs, and resembling in almost all respects in their morphology the gonococci. They are not, however, as a rule found in groups of four, as the gonococci frequently are. We also have a distinguishing mark for the gonococci by their reaction with staining agents. All of the pus organisms retain their color after staining by the Gram method. The organisms found in this case were all decolorized. Although the pus organisms are frequently found in cells, this is not their exclusive position. In any case where they are found in the cells they will be found in the tissue also, not contained in cells. The organisms found in this case conform with the gonococci, in that they were all decolorized by the Gram staining, and were only found in the cells. Moreover, the lesions which were produced were not such as we would expect to be produced by the pus organisms, or even by the pneumococci. Clinically the course of disease, especially the absence of fever, which almost all observers have noted a characteristic of the secondary gonorrhœal affections, also speak in favor of a gonorrhœal instead of a purulent infection. In this case, in spite of the extensive involvement of the joints and of the heart, there was almost an entire absence of fever. In cases of purulent infection, as we ordinarily see it, we do not have these same typical metastases which we have in gonorrhœa.

There is no reason why an ordinary purulent infection, which takes place from the urethra, should be localized in the joints or in the pericardium. I think that, apart from the direct objective facts which point in favor of the secondary gonorrhœal affections being due to infection with gonococci, a general consideration of the subject will also incline us to this belief.

DISCUSSION.

DR. FITZ: Dr. Councilman has given us all the facts in this remarkable case. He was kind enough to show me the specimens. I have no recollection of ever seeing a case like it, although one is tolerably familiar with cases of secondary infection through embolism from urethral disease, especially in consequence of surgical operations. I think, now that Dr. Councilman has called our attention to the possibility of this camplication, we certainly shall appreciate more thoroughly than we have been in the habit of doing, that even a fatal disturbance may result from gonorrhœa. A somewhat similar case I have seen in a recent medical journal, but Dr. Councilman's case is the first which has been called to my personal observation.

DR. LOOMIS: I have a case in mind which was misleading, due to a mixed infection. The gentleman had gonorrhœa for four or five weeks, and then suddenly developed an endocarditis, as determined by physical examination only, but the signs were very well marked. Soon after, within twenty-four hours, he had pains in his joints that had not existed before. A little girl, a relative, in the same house, at the same time came down with diphtheria, and in two or three days after the development of his endocarditis the man had a diphtheritic spot. He recovered, but if he had not had the evidences of diphtheria, and if the diphtheria had not occurred in the house, I should have been inclined to have regarded his endocarditis as of gonorrhœal origin.

DR. COUNCILMAN: The case Dr. Fitz refers to in the literature, I think, is the one which I quoted, by His. In tha tcase an endocarditis developed in the course of gonorrhœa, and the patient had small ecchymoses in various portions of his body, had infarctions in the spleen, etc. In that case, however, there were thrombi about the base of the bladder, and the infection was probably from that.

ACUTE FOLLICULAR TONSILLITIS.

By STARLING LOVING, M.D.,
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This disease is known by various names, as acute follicular tonsillitis, infectious acute follicular tonsillitis, more commonly as diphtheritic sore-throat, mild diphtheria, diphtheroid sore-throat, and ulcerated sore-throat, a circumstance sufficiently suggestive of the uncertainty which exists in regard to its true nature.

I would define it as an acute, febrile, specific, contagious-infectious disorder, wholly different from diphtheria, having its origin in the influences of pyogenic bacteria, staphylococci and streptococci, which may in all cases be found in the affected crypts of the tonsils, and particularly staphylococci, characterized by a peculiar inflammation of the tonsils involving the follicles, and the formation, in the follicles, of a more or less abundant yellowish-white exudation.

It appears to have been known for a century. Maygan, of France, described an epidemic which prevailed in that country in the year 1818, and accounts are to be found in various works written since that time. It was described by Wagner, McKenzie, Austin Flint, Bosworth, and later by Osler and others. Flint's description is quite accurate, but brief. He thought it possibly of specific origin. Bosworth's is fine, but faulty in that, though it may spread from individual to individual and assume the epidemic form, he does not consider it contagious. Dr. Osler's is too short. Other modern writers do not mention it. Since 1886, many papers have been published in the journals here and in Europe, among the most notable of which are those of Professor Frederici, of Florence; Dr. Gabbi, of Florence; Richardiere, of Paris; Schnell, of Marseilles; Boucseim, of Baltimore; Prince, of Boston; Hunt, of Illinois, and Park, of New York. All of the gentlemen named except Dr. Park take the ground

that the disease is idiopathic in character, while others, as Drs. Jacobi and Satterthwaite, of New York, equally eminent, declare it to be a modified type of diphtheria.

All English writers whose works I have had the opportunity to examine seem inclined to the belief that it may be specific, and that it has its origin in something, which they do not define, generated through the influences of defective drainage, or of bad ventilation and defective drainage combined.

The disease is of sufficiently common occurrence here and elsewhere. It seems to be more prevalent in France and in Italy, than in England or Germany, but it is very well known in the countries last named. Judging from communications to the journals, it seems to be of more frequent occurrence in the eastern and middle portions of our own country, than in the southern and far western, though Dr. Ely McClelland described a fatal case which occurred in Idaho. It is one of the commonest of all diseases in Central Ohio.

Like scarlatina, measles, whooping-cough, cerebro-spinal fever, and other acute contagious maladies, it prevails most in the changeable weather of late autumn, early winter, and of the spring.

The larger number of its subjects are children, youths, and young adults. Nursing infants and people of advanced age are less susceptible, but no class escapes entirely. In the month of January last I saw a typical case in a woman of seventy years. Persons suffering from chronic diseases of the nasal passages, of the pharynx, and especially of the tonsils, are possibly predisposed to this as to some other acute maladies, such as diphtheria; but those in good health appear equally susceptible. It attacks persons in all stations in life, the well-to-do and the cleanly, the poor and the negligent, alike, but the larger number are found among those who are obliged to live in unclean houses and foul air. In schools, reformatories, and in crowded tenements, having gained entrance, it often spreads rapidly and assumes the epidemic form.

English writers, as already stated, lay much stress upon the influence of bad drainage and emanations from sewers; and their reasoning is good in that filth predisposes to this as to other distempers, and affords lodgment for pathogenic germs. But the disease is often seen in habitations wherein cleanliness is the rule.

The remarkable uniformity of the symptoms, local and general, and

of the course of the disease (as seen here), and the rapidity with which it spreads from individual to individual, with the tendency, which, under favorable circumstances, it constantly exhibits, to assume the epidemic type, all point to specific character, and to contagiousness. All truly epidemic diseases are contagious, and this is not an exception. Few who have watched the independent origin and the spread of the disease from one member of a family to another, until all have been affected and a circumscribed epidemic developed, can doubt that a contagious disorder is under observation. An illustration may be allowable :

In April of the present year, a young man, a member of a family of six, was seized with tonsillitis at his boarding school, some miles from his home, where there were other cases. He went home to be nursed by his sister, a healthy young married woman of twenty-six years. His case was a typical one, with the ordinary symptoms. The disease ran the usual course and terminated favorably. On the sixth day after his arrival home, the sister became ill and exhibited the same symptoms from which he had suffered. On the day following (the seventh) the servant maid, aged twenty years, was attacked, and on the eighth day, a little girl of five years became ill. Two younger children, the older two years, and the younger two months of age, escaped. Previously to the coming of the young man no member of the family was ill, and there were no cases of sore-throat from any cause in the neighborhood. During the illness of the little girl, a neighbor, a woman with six children, visited the house, fondled her for a few minutes, and returned directly home, a square or two away, where, within twelve days, there were five cases of the malady.

Examples of the same tenor have been given by Drs. Dunlop and Prince, who cite the Rugby epidemic; and by Drs. Schnell, Boucseim, Descoings, and others.

There can be no doubt that it is conveyed by emanations and by contact; and some cases described by Dr. Boucseim furnish strong evidence that it is communicable by inoculation, and that, after being thus developed, it may be transmitted again, through contact and emanations. All who believe it to be a type of diphtheria, of course, acknowledge its contagious character.

The nature of the contagion has not been definitely settled, but the concurrent testimony of many observers, among them Fraenkel, Frederici, Gabbi, Schnell, and Richardiere, goes to prove that it lies in the presence and influences of pyogenic bacteria, staphylococci

and streptococci, in the crypts of the tonsils. Gaining lodgment, these organisms, increasing in numbers, produce, by presence alone, by poisonous secretions, or by inducing the formation of ptomaines, or toxalbumins, first local, and quickly afterward, systemic disturbance.

During the month of April and the early part of the present month, using sterilized swabs and tubes, I collected specimens of the exudation from twenty-four typical cases, and, in order to have the investigation free from bias, submitted them to Dr. J. C. Graham, a skilful bacteriologist, for examination. Dr. Graham found, with the bacteria ordinarily present in the mouth and throat, staphylococci, staphylococcus pyogenes aureus, albus, citreus, and streptococci (the staphylococci most abundant) in every case, but no other pathogenic germs —nothing resembling the Klebs-Loeffler nor the pneumococcus of Fraenkel. Although the number of cases examined was not large, the uniformity of the results would seem conclusive.

The anatomical changes, so far as I have observed, with a few notable exceptions, consist in the peculiar inflammation of the tonsils, with the exudation, inflammation and swelling of the glands at the angles of the jaws, one or both. I have occasionally seen suppuration of one or both tonsils and inflammation of the middle ear occur as complications. In one case convulsions and in another what I judged to be septicæmia developed after the exudation had nearly disappeared, but I have never encountered other formidable complications, as endocarditis, pleuritis, pneumonia, rheumatism, orchitis, etc., which appear to be so common in Europe, nor have I seen paralysis of any part accompanying or as a sequel. The urine is frequently albuminous during the height of the fever, and for a few days afterward, but becomes normal with convalescence. To judge from the writings of numerous European observers, the disease must be much more severe with them than here, particularly in France and Italy. Possibly the difference may be accounted for by the better conditions of life in the United States.

The period of incubation varies between three and ten days, the difference arising, seemingly, from degrees of susceptibility, exposure and concentration of the virus.

The course of the malady is nearly uniform. The symptoms differ in severity, but in no other respect.

In a minority of cases there is a prodromic stage of twelve or twenty-four hours, marked by feverishness, lassitude and general discomfort, but in the larger number the attack is abrupt. There are rigors, or a decided chill, followed speedily by fever ranging from 102°, 103°, 104°, to 105.5°, and even to 106° F., flushed face, more or less intolerance of light, headache, severe pain in the loins and extremities, most severe in the back and in the legs, but unpleasantly so in the arms and shoulders (patients often complaining that they ache all over), with a feeling of weariness and prostration. The skin is hot and dry, but not so devoid of moisture as in some other febrile diseases. The pulse is accelerated to 100–110, or 115, is somewhat enfeebled, soft and compressible. The tongue is coated with a thick, soft, whitish-yellow fur, the appetite is diminished or lost, there is thirst, and occasionally, but occasionally only, nausea and vomiting. The urine is scanty and highly colored, and sometimes albuminous. The bowels are almost uniformly constipated, but are easily moved.

Sometimes before, but more commonly simultaneously with the fever and its concomitants, patients complain of sore-throat and pain in swallowing. These symptoms are not severe, usually, but they are seldom absent.

In this, as in some other respects, the disease appears to be milder here than in Europe where, according to Richardiere, Laborderie, and Schnell, pain in the throat and difficult deglutition are very great. In rare cases the local symptoms are not developed until twelve or fourteen hours after the appearance of the fever, but they are always developed.

When the throat is examined the pharynx and soft palate are found to be hyperæmic or inflamed and somewhat swollen. The tonsils, one or both, generally both, are found enlarged and inflamed, and their surfaces bright red. The lacunæ are prominent and dilated, and from three to ten of each organ filled with a yellowish-white exudation, which overlaps their borders and extends a short distance over the surrounding mucous membrane. In most cases it is distinctly circumscribed, and confined to the outlet of the follicle and to the parts in its immediate vicinity. It is not attached to the mucous membrane, and may be easily removed. If scraped away twenty-eight or thirty hours after its appearance, no hemorrhage follows, as happens when the membrane is pulled away during

the earlier progress of diphtheria, nor is the surface of the mucous membrane ulcerated and eroded as in diphtheria. On the second day the exudation is somewhat more abundant and more distinctly bounded. On the third day it has become less, and, in a large proportion of cases, by the end of the fourth day it has disappeared, leaving the tonsils swollen, red and sore, and the crypts more patulous than in the normal state. During the twenty-four hours following, the patient often complains as much or more of pain in the throat and of difficulty in swallowing than before.

Now and then a case is seen in which the exudation is more extensive. The points, or dots, filling and overrunning the crypts, assume the form of patches, which may coalesce, cover the tonsils, and form a membrane somewhat resembling that of diphtheria.

It is, however, never quite so extensive, is confined to the tonsils, shows no tendency to spread beyond, and, unlike the membrane of diphtheria, which is always thickest in the centre, it is thinner at the lines of junction, and is dotted over with islets or points, which mark the mouths or openings of the inflamed crypts. More often, instead of a membrane, the tonsillar surface between the involved crypts is covered with a film of muco-pus. At any time during the continuance of the exudation a probe may be pushed through the thicker points into the follicle behind, a fact which is regarded by Dr. Bosworth as highly diagnostic.

The glands at the angles of the jaws, and the submaxillary glands, in many cases become inflamed and swollen, and usually the patient complains of a degree of stiffness of the neck, but the glands never suppurate, nor is the extensive infiltration of the connective tissue of the neck, which is of such common occurrence in diphtheria, scarlatina, and the severe type of suppurative tonsillitis, ever seen. The swelling of the tonsils is sometimes sufficiently great to make those organs almost as prominent outside as inside the throat, but, like the swelling of the neighboring glands, it usually disappears soon after the fever.

On the third or fourth day (in mild cases sometimes at the end of the second day) the patient is better. The fever is less, the skin becomes moist, the headache and muscular pain cease, the exudation disappears, the tongue is less furred, there is freer secretion of urine, and though the patient still complains of his throat, and feels weak,

exhausted, and often despondent, convalescence has begun. But the patient remains weak, pallid, and disabled for many days after the disappearance of all active symptoms.

Few maladies of such brief duration cause greater depression of muscular strength, more disturbance of the nutritive functions, or a greater degree of anemia.

The diagnosis is the most important point in the consideration of the disease. It is especially important that it be accurately discriminated from diphtheria, with which it is so often confounded.

With the microscope and culture the diagnosis is easy and positive; but not every one has a microscope nor understands its uses sufficiently well; not every one is sufficiently acquainted with the science of bacteriology to distinguish readily between the various organisms which are found in the body, and give to them their proper place among etiological factors. Besides, it is often desirable and necessary to pronounce an unqualified diagnosis, to know reasonably well the character of a case in hand without delay.

Neither follicular tonsillitis nor diphtheria in ordinary course has marked prodromic symptoms. Dr. A. Thompson states that in diphtheria there "may be a brief prodromic stage which may last only twenty to thirty-six hours, or it may 'occupy' a week." Commonly it does not "occupy" twenty-four hours. Oftener there is no prodromic stage, the disease, like follicular tonsillitis, beginning abruptly.

Both diseases begin with rigors, or a chill, which with the succeeding fever, are often more pronounced in the milder disease. "The temperature of diphtheria may in a day or two reach 104° F., but in many cases as low as 102.5° F. throughout the attack." (Thompson.) The course of the fever in diphtheria, like other symptoms, is irregular, the temperature rising and falling, but high temperature is not characteristic of that disease. In tonsillitis, a temperature of 103°, 105°, or 106°, is often observed within twelve hours after the invasion, continues without material change, until defervescence, and does not return unless a complication arises.

The pulse in diphtheria is more frequent and more feeble than in tonsillitis. It ranges between 110 and 120, though the fever is not above 103° F. The sounds of the heart are not changed in tonsillitis. In diphtheria the impulse is enfeebled and the first sound often indis-

tinct from an early period. The pulse in tonsillitis ranges from 100 to 115 accordingly as the fever is intense; but, while its strength is diminished, it is not so weak as in diphtheria.

In neither disease are the respiratory movements greatly disturbed, but in diphtheria, as the case progresses, they become feeble and quickened, or very slow.

In both diseases there are headache, more severe in diphtheria, and muscular pains, more severe in tonsillitis.

The local symptoms differ, even before the formation of the exudate. In tonsillitis, while the entire throat is hyperæmic, generally the tonsils alone are inflamed, and in equal degree, but the inflammation shows no tendency to invade other parts.

In diphtheria the inflammation begins oftenest on the tonsillar surfaces, but not infrequently it appears simultaneously in other parts, and when the case is to be severe the whole faucial surface, the soft palate, and the nasal passages, may become involved.

In diphtheria the inflamed parts have a darker hue than in tonsillitis, and present a smooth, glistening appearance, as though coated with a transparent varnish, and are irregularly dotted with somewhat elevated, shining points, which, according to Oertel, are nests, or colonies, of bacteria. At this stage the pain in swallowing is often greater in the milder disease.

In tonsillitis the exudation appears at several points in the openings of such of the follicles as happen to be implicated, and seldom extends far beyond. When, as happens in exceptional cases, it extends and forms a continuous membrane, the inflamed follicles may each be distinguished by islets of denser exudation.

The exudation, or slough, of diphtheria appears at one or two, or three or four points, and spreads, usually, until the original points coalesce, cover the tonsil, and often the neighboring parts. In many cases the tonsils, the pharynx and soft palate are covered, and the nasal passages are filled. It is always thick at the centre, is homogeneous in appearance, at first ivory-white in color, but becomes grayish, then gray, and when separation begins, blackish or black, especially at the edges, from the oozing of blood from the ulcerated mucous membrane beneath.

In a large proportion of cases, unfortunately, the larynx and trachea become implicated. Such cases often appear mild, and the

air passages are not affected until after the acute stage has passed in the parts above.

In many cases in which the larynx and the trachea are involved there is inflammation, but no membrane is formed in the throat, and suspicion of diphtheria is first excited by croupy cough and dyspnœa. The respiratory apparatus is not affected in tonsillitis.

The exudation of follicular tonsillitis consists of the changed secretion of the tonsillar crypts, with an admixture of epithelial scales, fibrin, and leucocytes. Staphylococci and streptococci are abundant, but no other pathogenic germs are found.

The false membrane of diphtheria consists of the necrosed epithelial layer of the mucous membrane, of fibrin, of fatty matter, leucocytes, and various bacteria, among which are staphylococci and streptococci, and the specific Klebs-Loeffler bacillus. There is no report of the finding of the Klebs-Loeffler bacillus in any typical case of follicular tonsillitis.

All who have watched the progress of diphtheria have learned to dread relapses. In many cases, when every indication points to convalescence, there will occur a rigor, an accession of fever, an increase or renewal of pain in the throat, and a fresh membrane presently appears, frequently in a new locality.

Relapses never occur in tonsillitis, nor does the exudation re-form when once it has disappeared.

In diphtheria there is always fetor of the breath, a muffled or nasal voice, and noisy breathing—symptoms never observed in tonsillitis.

Both diseases cause sudden and great debility, and marked anæmia; tonsillitis more quickly but less profound than diphtheria.

Convalescence from both is slow. From tonsillitis it begins after the cessation of fever, is steadily progressive, and finally complete. In this country complications and sequels are uncommon. Months often elapse before the restoration of health after diphtheria, and the victim is constantly liable to paralysis, to hemorrhages, abscesses, swollen glands, nephritis, and other miseries which do not follow tonsillitis.

Neither disease protects against itself.

In some cases of scarlatina, before the eruption, the tonsils and pharynx present somewhat the same appearance as in tonsillitis, but there is less swelling of the tonsils, the inflammation is more diffused,

the inflamed parts are of darker hue, the sloughs are larger, gray in color, instead of yellowish-white, spread rapidly, and soon coalesce. The great frequency of the pulse, the pungent heat of the skin, together with the cerebral vomiting so characteristic of scarlet fever, serve as guides until the appearance of eruption decides the nature of the case.

The inflammation of the fauces, which forms a part of the eruption of measles, is not likely to be mistaken for follicular tonsillitis, and the latter is sometimes intercurrent with the former disease.

Acute superficial, and deep peri-tonsillitis, or quinsy, generally confined to one side, is as likely to occur at one season as at another, and is never attended with the formation of an exudation or false membrane.

Membranous or herpetic sore throat, which appears to be common in some localities, but which is of rare occurrence in Ohio, is "distinguished by vesicles upon the tonsils, in the pharynx, on the soft and hard palate, isolated, or in groups, surrounded by zones of inflammation," and, by the appearance, in many cases, of similar vesicles at some part of the inner surface of the cheeks, the lips, at the corners of the mouth, or upon the face, and by the fact that when the vesicles burst they are soon covered by the formation of a grayish-white, or yellowish-white membrane, which extends and not infrequently covers tonsils and the neighboring parts. It is generally more prolonged, and has more decided prodromic symptoms than follicular tonsillitis, and is attended with much less fever.

The history, the general appearance of the patient, cicatrices or lesions in various parts, especially of the fauces, and of the tongue, suffice to distinguish cases in which the tonsils have become diseased through syphilitic infection.

Chronic follicular tonsillitis may easily be discriminated from the acute form by its protracted course and by the absence of febrile symptoms. It would be difficult to discriminate from the appearance of the tonsil alone.

The prognosis of the disease as it prevails in Ohio where, when recognized, it is considered a comparatively slight malady, is favorable, but while a favorable termination is ordinarily to be expected, unpleasant contingencies should be borne in mind. Within six months I have had two cases in which, quite unexpectedly, very

grave symptoms were developed. In the one, the patient, a healthy but neurotic young man of twenty-six years, on the second day of disease there occurred four epileptiform convulsions, following each other in quick succession, caused, as I thought, by the intensity of the fever (105.5° F.) and the severity of the pain. The convulsions were controlled by the influence of chloroform, the pain and the fever by hypodermatic injections of morphine, and full doses of aconite, and recovery was perfect.

The second patient was a strong healthy boy of twelve years who had never been ill before. On the morning of the fourth day of the attack, after the exudation had almost disappeared, and the temperature had fallen to 99° F., there was a chill, followed by fever, which ranged irregularly between 102°, and 105.5° F., for eight days following. The skin was hot and dry, or hot and bathed in sweat. There was delirium alternating with stupor, the tongue was coated and dry, there was thirst and slight nausea, incontinence of urine, alternating diarrhœa and constipation, both the liver and the spleen were somewhat enlarged and tender, and there was slight jaundice. There was cough with moist râles, the pulse was frequent and feeble, but the sounds of the heart though weak, especially the first sound, were normal. The urine was slightly albuminous. At the end of the eighth day there was sudden defervescence. The temperature fell within four hours from 104° F., to 97° F., and to 96° F., and remained as low as 97° in the morning, throughout the four following days, during which time it was never above 98° F. After the subsidence of the fever the patient became rational, and throughout the period of depression declared he was well. The functions of his vasomotor system gradually gained strength, the recovery was perfect. I judged the case to be one of toxic fever, having origin through material absorbed from the tonsils. It gave me much anxiety, especially as I had assured the parents in the beginning that there was no danger, and that the boy would be well in the course of a week.

Especial pains should be taken to discriminate between tonsillitis and diphtheria, as error makes correct forecast impossible, and is certain to be followed by unpleasant consequences. When, as not infrequently happens, a case of diphtheria is mistaken for one of tonsillitis, and some one or other of the numerous perils of the former

disorder presently appear, or, though the original case ends favorably, should the infection spread, and a malignant case develop in another member of the family, explanations would be somewhat awkward and difficult.

When the milder disease is mistaken for the more severe, unsuitable treatment is prescribed, and much unnecessary alarm and inconvenience result from the restrictions in regard to contagious maladies now almost universally enforced.

The similarity between the symptoms of the two diseases is often taken advantage of by dishonorable and designing men, who frequently boast that they have treated, by some extraordinary method, a hundred or two cases of diphtheria without loss.

Whenever one reads or hears of such extraordinary results, whether honestly or dishonestly reported, there is room for the suspicion that a false prognosis has been based upon an equally false diagnosis.

The indications for treatment are few and sufficiently simple, but, unpleasant possibilities in view, they should in all cases be promptly met, and the means vigorously applied. They consist in measures for the cleansing of the throat and the application of remedies for the reduction of fever and the relief of suffering.

To meet the first, the application of sodium bicarbonate, chlorine water, peroxide of hydrogen, sodium salicylate, potassium bromide, are all recommended and used.

I prefer a solution of the potassium bromide (one ounce to one pint), alternating with the peroxide of hydrogen, diluted with an equal quantity of water, used as gargles, or better, when practicable, applied by the use of a spray apparatus.

For the reduction of fever a cold bath, or better a cold pack, repeated if occasion requires, with moderate doses of aconite and morphia, codeia (codeia is better when the patient is a child) or other preparation of opium. Antipyrine, antifebrine, phenacetine, etc., are liked and prescribed by many practitioners, and there can be no question as to their antipyretic effect; but any one who has seen the dangerous depression and severe cyanosis which not infrequently follow even moderate doses of these medicines will hesitate before prescribing them under circumstances not involving danger to life.

Purgatives are not often indicated, but a laxative in the beginning of the treatment is beneficial.

After the subsidence of the fever, a tonic regimen with tonic medicines, as the vegetable bitters, such as chiretta, calumba, the extract of St. Ignatius bean, nux vomica, or strychnia, and some preparation of iron, are decidedly indicated. Of the bitters I prefer the St. Ignatius bean, and of the preparations of iron the potassio-tartrate, or the mixture of iron and acetate of ammonia.

It is of minor importance, but, if idiopathic, as seems to be the case, the disease should have a distinctive appellation and a place in nosology. Possibly the name Infective Acute Follicular Tonsillitis is sufficiently distinctive, but I venture to propose Tonsillar Fever as more so.

DISCUSSION.

DR. WHITTAKER: Dr. Loving has given us a very fine picture of a very familiar disease. I am sure that every one of us has felt anxious moments in looking into a throat to know whether we shall call it a simple catarrhal disease or diphtheria, if it be acute, or catarrhal or syphilitic if it is a chronic form. We all become so familiar with this disease in the course of time that a glance usually enables us to make the diagnosis. I would rather rely upon the statements of a good clinician in regard to the diagnosis than that of any ordinary bacteriologist. Baginsky has recently made an important observation that there are two forms of diphtheria, one benign and the other malign—one due to common pyogenic organisms and the other to the organism of Loeffler. While it is possible to establish the presence of the Klebs-Loeffler bacillus by culture in twenty-four hours, it takes a skilled worker to do it. Most of us have to rely upon clinical evidence, and that is so distinctive as, for the most part, to enable us to distinguish the disease.

DR. MASON: I suppose it is determined that this disease is not diphtheria, both from its history and bacteriology; but I must confess that many times I have been obliged to tell anxious parents that I must wait before expressing an opinion. This is easier to do now than it was formerly, from the fact that the laity more generally recognize the importance of bacterial culture in doubtful cases. That this is by no means an imaginary difficulty is shown by the following facts: In the Boston City Hospital we have a diphtheria ward, to which there have been admitted during the last two and a half years 750 cases of diphtheria. During the same time there have been sent to this ward by out-

side practitioners 120 cases of supposed diphtheria which turned out to be simple tonsillitis. The admitting physicians of the hospital were unwilling in these cases to take the resposibility of refusing admission, and it was only after the lapse of a day or two that cultures and observation determined the true nature of the disease. Another fact in that connection was that no one of these 120 cases of non-diphtheritic tonsillitis developed diphtheria, although they were exposed to that disease, as our facilities for complete isolation were not perfect. This shows, I take it, not that this follicular tonsillitis confers immunity to diphtheria, but that the danger to older children and to adults, as many of these patients were, is comparatively little when they are exposed to diphtheria. The exposure was not extreme, because such cases were isolated as far as they could be in separate rooms adjoining the diphtheria wards.

SARCOMA OF THE RIGHT LUNG DIAGNOSTICATED DURING LIFE BY THE USE OF THE MICROSCOPE; SECONDARY TO SARCOMA OF THE TESTICLE WHICH HAD BEEN REMOVED FOUR YEARS PREVIOUSLY.

By D. W. PRENTISS, M.D.,
OF WASHINGTON, D. C.

N. H. H. was fifty-one years old. His parents had been healthy. His father was killed in a saw-mill. His mother died of pneumonia, aged sixty-three years. There was no history of malignant disease or of tuberculosis in the family. The man's health had been failing for five years.

When a child he injured his testicle, and again later when riding; but this never troubled him. Five years before his last illness the testicle was again hurt, when it became inflamed and the man was confined to bed for some time, suffering great pain. After this he had to exercise great care of the organ. The testicle was removed four years previous to death by Dr. J. Ford Thompson, who pronounced it sarcomatous.

Pulmonary symptoms appeared in August, 1890. The man had had a very profuse hemorrhage from the bowels in January, 1890. He complained of great pain in the right side over the liver; slight cough; and bloody sputa. No large hemorrhage from the lungs occurred. The sputa were frothy, stained with blood, and occasionally mixed with a fibrinous substance.

I first saw the patient March 29, 1891. He had been under the care of a sectarian practitioner, and had been treated for pulmonary tuberculosis for about nine months.

When I saw him he was greatly emaciated; suffering with pain in the right side of the chest; and coughing and expectorating bloody sputa. At first sight he presented all the appearances of tuberculosis. Physical examination, however, showed a condition evidently not due to pulmonary tuberculosis. The left lung appeared normal on auscultation and percussion. The right lung was solid throughout nearly its entire extent. Air could only be heard to enter the lung in two small areas, one near the apex and another low down in front in the lower lobe. At these points at the autopsy were found respectively a little normal lung-tissue and a small cavity resulting from the breaking

down of the diseased tissue. The sputum was sent to Dr. Theobald Smith for examination for tubercle bacilli, but none were found.

The principal symptoms in the case were the cough and expectoration, great pain in the side from the pleuritic extension of the disease, extreme emaciation, and exhaustion. Decubitus was mostly left-sided. As the case progressed bedsores developed over the hips and sacrum, which added greatly to the patient's suffering.

Treatment was symptomatic—except that at the first the man was put on a mixed specific treatment of potassium iodide and mercuric chloride. There was no clinical evidence of specific disease, but upon a suspicion that there might possibly be a syphilitic taint this treatment was tried. It was continued for about three weeks without effect. Other treatment consisted of morphine —to relieve pain—stimulants, and tonics.

The right side of the chest was enlarged and the intercostal spaces obliterated. Dr. J. Ford Thompson was called in consultation and the side aspirated, to determine if there was liquid in the pleural cavity. None was found, but instead, only blood and a quantity of substance looking like partially organized fibrin was drawn out, evidently from the lung-substance. This substance was sent to Dr. Theobald Smith for microscopic examination, and reported by him to be composed of masses of sarcoma cells.

Up to this time malignant disease of the lung had not been thought of, but the diagnosis now became clear, especially when inquiry brought out the fact that a sarcomatous testicle had been removed four years before. The patient died of exhaustion, August 21, 1891, one year after the first symptoms of lung-disease developed.

The autopsy was held four and a half hours after death by Dr. Robert E. Edes. Emaciation was most extreme. The whole right lung was sarcomatous. There was a pus cavity at the lower border containing about two ounces of pus. Nearly the whole lung was bound to the chest wall and to the diaphragm by strong adhesions. The fourth, fifth, sixth, and seventh ribs were eroded posteriorly by pressure. The upper part of the right lung contained several patches of healthy tissue anteriorly, but the remainder of the lung was replaced by sarcomatous tissue, old hardened blood-clots, and fibrin. The left lung was healthy, except in the upper part of the lower lobe, which was solidified and grayish in appearance. The right kidney was normal; the left kidney congested, otherwise normal. The spleen was small, but normal. The intestines were normal. There was no enlargement of the lymphatic glands of the abdomen. The liver was normal. The gall-bladder was full of bile. The heart was small and flabby.

Dr. W. M. Gray, Microscopist, Army Medical Museum, made the following report of the microscopic examination:

"Microscopic examination of sections of the supposed sarcomatous testicle and lung proves the growth to be the same in each organ. The sarcoma is of the variety known as lympho-sarcoma. The sections will not take an intense nuclear staining, which is doubtless due to slight post-mortem degeneration."

I have been influenced to report this case on account of its comparative rarity, especially in private practice, and also as illustrating the value and importance of the microscope in diagnosis.

As to its rarity, this is the only case I have seen in a private practice of thirty years; although hospital statistics show malignant disease of the lungs not to be uncommon.

When only one lung is affected it is more frequently the right, in the proportion of 2 to 1. Walshe records 29 cases of primary malignant disease of the lung, in only 18 cases of which one lung was affected, and of these 18 the right 13 times and the left 5 times. Kohler reports 31 cases, one lung being affected in only 23; the right 15 times; the left 8 times. The condition is more common in men than in women. Hasse reports 22 cases; 17 in men, 5 in women. (*Ziemssen's Cyclopœdia*, vol. v. p. 436.) Osler, however, states that malignant disease of the lung is more common in women.

Malignant disease of the lung is principally to be differentiated from tuberculosis. The possibility of syphilis should not be overlooked.

DIFFERENTIATION FROM TUBERCULOSIS.

TUBERCULOSIS.	MALIGNANT DISEASE.
Begins usually at apex of left lung, and extends to right lung.	Begins usually in middle lobe of right lung.
Sputa muco-purulent, nummular.	Sputa gelatiniform, mixed with pus and blood, "prune juice."
Cavities.	Intense dulness over whole lung.
	Swelling of lymphatic glands more marked.
Tuberculous diathesis.	Previous history of malignant disease, as in breasts or testicles.
Tubercle bacilli.	Sarcomatous or carcinomatous cells.

The only other condition that produces the same extent of intense dulness in the lung is a large collection of fluid in the pleural cavity. This is recognized, of course, by aspiration.

As to syphilis of the lung, its extreme rarity alone is almost enough to set it aside.

Tuberculosis of the lung in a syphilitic subject is common enough —in fact, a distinguished syphilographer (Dr. Taylor, of New York) stated recently that the two diseases go hand-in-hand; that syphilis

precipitated pulmonary tuberculosis in a predisposed patient. But syphilis of the lung, as a distinct form of disease, does, however, exist, many cases having been reported, and the early symptoms are much like those of malignant disease of the lungs. The diagnosis may be determined by the therapeutic test.

Finally, it is worth noticing that a man could live, as this one did for months, with such an extent of disease within the chest-walls.

DISCUSSION.

DR. WELCH: Was the diagnosis made during life by Dr. Smith from fluid withdrawn by means of an aspirator?

DR. SMITH: The material came to me in a small phial, which was half full of blood-stained serum. In this serum were floating small, gelatinous, grayish-white masses, perhaps as large as a match and half as long. These, under the microscope, were made up of cells entirely different from pus-cells and about the size of leucocytes. The nucleus was vesicular. In these gelatinous masses there were seen single and branched capillaries, and, taking these few facts into consideration, I suggested to Dr. Prentiss that possibly the case might be sarcoma.

DR. WELCH: The point is interesting as to the possibility of making a diagnosis of malignant tumor of the lung from an examination of material withdrawn by aspiration.

DR. PRENTISS: This fluid was aspirated directly from the lungs and we found afterward there was no pleural cavity.

DR. TRUDEAU: I had a case like this once in which I succeeded in making a diagnosis by negative inoculation experiments. Upon inoculating guinea-pigs with fluid and sputum drawn from the chest, with negative results, the diagnosis of probable cancer was made.

DR. LOOMIS: I should think that the fact that the lung had been solidified over such a period of time without involvement of the other side would have made it almost certain that it was not tuberculosis.

PULSATING PLEURAL EFFUSION.

By J. C. WILSON, M.D.,
PROFESSOR OF THE PRACTICE OF MEDICINE AND OF CLINICAL MEDICINE IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

I HAVE had the opportunity of studying three cases of pulsating pleural effusion. The first I reported to the Philadelphia County Medical Society on May 8, 1889. The report is embodied in the *Transactions* of the Society, but was not published elsewhere. As the case illustrates some unusual phases in this interesting condition, I have incorporated the report in this paper. The other cases are now published for the first time.

CASE I. *Strain in lifting; pain in the left side; pleural effusion, at first serous, subsequently purulent; extensive pulsation of the side; pyo-pneumothorax; paracentesis thoracis; free drainage, interrupted by removal of tube; tense pneumothorax; resection of ribs; recovery.*—The patient was a male, aged twenty years, unmarried, Irish, a laborer in a dye-house. He was admitted to St. Agnes's Hospital March 16, 1889. His parents were living and in good health. Three years previously the patient had an attack of chest-trouble, which continued for four weeks. Subsequently his health had been good.

About six weeks prior to admission to the hospital, in lifting a large roll of cloth, he suffered a twist of the left side. He immediately experienced severe pain, which was increased on deep breathing. There was at first no cough. After a time he began to suffer from shortness of breath and from cough unattended by expectoration, but worse at night; he was able at all times to lie down in bed. The difficulty in breathing becoming urgent, his chest was tapped on three occasions during the nine days prior to his coming into the hospital, a large quantity of fluid being removed. This fluid, he stated, was at the first two tappings clear, but on the last occasion turbid.

Upon admission the presence of a large pleural effusion upon the left side was determined without difficulty. The cardiac impulse was felt on the right side in the nipple line, and was visible in the third and fourth intercostal spaces to the right of the sternum; there were no murmurs. There was a distinct impulse having the cardiac rhythm over the whole of the left side anteriorly and laterally as far as the line of the posterior axillary fold. This impulse,

which was very distinct upon palpation, was not visible; it was not felt posteriorly.

Four days later, aspiration was performed, the needle being introduced in the eighth intercostal space slightly in advance of the line of the posterior axillary fold. About three pints of foul-smelling greenish-yellow pus were withdrawn. Threatening symptoms arising, the aspiration was discontinued.

After two days the pulsation on the left side was no longer observed to the left of the nipple line, save in a restricted area in the third intercostal space. The fluid rapidly reaccumulated and pulsation returned. By means of a trocar four pints of fetid pus were evacuated; a soft-rubber drainage-tube was introduced, and the chest dressed antiseptically. Rapid improvement in the patient's general condition immediately followed. In a week he was up and about the ward. The discharge from the tube amounted to a few drachms only daily, and was no longer fetid.

After the lapse of three weeks the drainage-tube became clogged and was removed, but the resident physician was unable to replace it.

Owing to absence from the hospital, I did not again see the patient until a week later. The impulse of the heart was felt in the third and fourth intercostal spaces near the right nipple. The left chest was distinctly flattened in its antero posterior diameter, and there was again pulsation over its antero-lateral surface, extending to the posterior axillary line and synchronous with the cardiac systole. The pulsation was most distinct in the second and third intercostal spaces to the left of the nipple line, but could be faintly perceived at the base of the chest. The percussion-sounds were tympanitic anteriorly above the level of the fourth rib and flat below. Posteriorly percussion was flat.

The dyspnœa increasing and the substernal pains being more pronounced, the sixth, seventh, and eighth ribs were resected for an inch in the axillary line. Upon puncture of the pleura, there was an escape of air, and the wound being enlarged to permit of an examination of the cavity, it was found free from pus. The finger could reach the compressed lung, which transmitted the cardiac impulse; and a large probe, carried into the wound and gently brought in contact with the lung, moved synchronously with the cardiac systole. After the operation the heart did not return to its normal condition, but continued to beat to the right of the sternum. A large drainage-tube was introduced. Suppuration was re established and a small amount of pus continued to discharge by way of the drainage-tube. Distinct pulsation persisted over the upper part of the chest outside the mammillary line. The patient did well, and after a time left the hospital and was lost sight of.

The sequence of events in the foregoing case appears to have been the following: Strain in lifting, causing laceration of the pulmonary pleura (whether pleural adhesions, set up during the sickness three years before, had any part in determining such a lesion or not cannot be decided); pneumothorax, followed by serous effusion; aspiration in the fourth week, twice repeated at short intervals; pyo-pneumo-

thorax, with firm compresion of lung, the lower lobe of which was completely airless, and probably adherent to the pericardium; slight expansion of upper lobe after aspiration; heart dislocated and retained in its new position by inflammatory adhesion; transmission of impulse from the displaced heart through the contracted left lung, at first to the fluid contents, and later to tensely confined air in the pleural cavity, with pulsation of the chest-wall. This pulsation was more distinct and more persistent opposite the second and third intercostal spaces, being probably there transmitted through the compressed lower portion of the upper lobe, which had contracted adhesions at that point.

The tension within the pleural cavity, which, shortly after the removal of the first drainage-tube, gave rise to flatness on percussion below the area of the adherent lung, is only explicable upon the hypothesis of a persistent valve-like opening in the pulmomary pleura.

CASE II. *Croupous pneumonia of left side; pain in side; a month later signs of large effusion; pulsation; treatment by the method of Lewaschew, without success; free drainage; recovery.*—Samuel L., aged twenty-two years, a bookmaker, was admitted to a private room in the German Hospital, March 14, 1891. The family history was good as regards pulmonary disease. His mother had died of rheumatism; five brothers and sisters were all living and in good health. There was no history of tuberculosis in the family. Five weeks prior to admission the man had had left-sided pneumonia, accompanied at first by a great deal of pleural pain, and becoming after a time complicated with pleural effusion. The physician who attended him was unable to state at what period the signs of the effusion first appeared.

The effusion steadily augmented. The patient rapidly lost flesh and became much oppressed. On admission he was greatly emaciated, feeble, and anæmic; there was constant distressing cough, with a small amount of mucoid expectoration. The temperature ranged between 99° and 100.5°; the pulse, between 116 and 128; the respirations, between 20 and 24. The tongue was coated; the patient had complete loss of appetite; the bowels were constipated. Upon examination of the chest the physical signs of a large left-sided effusion were found present. There was flatness upon percussion over the whole chest in front and behind, except at the apex, where there was tympanitic resonance. The semilunar space was obliterated; the heart was displaced to the right side, the impulse being felt in the third and fourth intercostal spaces within the right mammillary line.

Upon auscultation, the heart-sounds were distinct. There were no murmurs. At the upper part of the chest on the left side, both anteriorly and posteriorly, was heard feeble bronchial respiration. Below the line of flatness this was

gradually lost. The vocal fremitus and vocal resonance were greatly diminished over the region of flatness. On the right side there was pleural respiration without râles. On the left side there was bulging of the lower intercostal spaces, together with distinct pulsation, perceptible both to the eye and to touch, synchronous with the heart's action, from the second intercostal space to the base of the chest, and extending, with gradually diminishing intensity, to the mid-axillary line, where it was lost. There was no pulsation posteriorly.

Careful examination was made for the signs of even a limited pneumothorax. Neither ordinary percussion nor the coin-test yielded the signs of such a condition. Succussion signs could not be elicited.

Aspirations were at once performed, and thirteen fluidounces of light-colored pus of creamy consistence were withdrawn. The patient was much agitated, and insisted upon the operation being discontinued. On the following day aspiration was repeated and eighty ounces of pus were evacuated. The pulsation thereupon disappeared and did not recur. This was followed by evidences of expansion of the lung, namely, vesicular murmur reaching as low as the angle of the scapula, with crepitant and sub-crepitant râles, vesicular resonance, friction sounds, and ægophony. The impulse of the heart could no longer be detected to the right of the sternum, but was felt at the left border of the sternum. The intercostal spaces were slightly retracted; the patient showed rapid improvement; the temperature fell; appetite returned; cough ceased. In the course of a few days, however, there were signs of reaccumulation of the effusion. It was then determined to treat the empyema by the method of Lewaschew, which consists in the removal of the pus and its replacement by sterilized normal salt-solution. This operation was repeated on several occasions at intervals of two or three days. It was not, however, attended with success, the pus always rapidly reaccumulating, and tending, after a time, to become foul.

On April 16th the chest was perforated by means of a short trocar of large diameter, and through the canula a No. 18 soft catheter was introduced and allowed to remain. The drainage thus secured was efficient.

On May 12th the drainage-tube, which had been gradually shortened was withdrawn, and at the end of May the patient left the hospital, well, with an absence of retraction of the chest-wall, which, under the circumstances, was remarkable. In a short time he resumed his profession as a gambler.

The chief interest in this case relates to the fact that neither in the history nor in the physical examination were there evidences of pneumothorax. The patient had been attended outside the hospital from the beginning of his sickness by a competent and painstaking physician, who recognized the attack as one of pneumonia, and gave a clear history of sudden onset, with chills, high fever, and rusty sputum. At no time in the course of the attack had there been such purulent expectoration as would justify the suspicion that a bronchial fistula

had been established, nor was there elicited upon painstaking search, even with the coin-test, the slightest indication of any collection of air in the pleural cavity. The case is of further interest because, immediately upon the reduction of the intrapleural tension, after the aspiration, the pulsation disappeared, not to recur when, as was shown to be the case during the treatment by the method of Lewaschew, pneumothorax had been accidentally established, nor when, after the perforation of the chest-wall, a free pyo-pneumothorax existed.

CASE III. *Family history of tuberculosis; influenza followed by pulmonary tuberculosis; large left-sided effusion; aspiration of purulent fluid; pyo-pneumothorax; pulsation; large tuberculous cavity of right lung; death from hemoptysis.*—W. B., twenty-one years of age, a harness-maker, was admitted to the hospital of Jefferson Medical College, October 15, 1892. His father had died of blood-spitting; his mother, from the results of influenza. He had one sister, who was living and in good health. Until two years previously the patient had been well and strong. At that time he had an attack of influenza, which was followed by rapid and serious failure of health; digestion became disordered; he lost weight and strength, and a troublesome cough developed. After the lapse of four months he began to suffer from afternoon fever; he became progressively weaker, and emaciation was marked. He suffered also from exhausting night-sweats, and on several occasions he had hemoptysis.

In July, 1892, he presented himself at the Out-patient Department of the hospital for treatment. It was then found that the left chest was full of fluid. Declining operative treatment, he discontinued attendance at the clinic. He states, however, that shortly afterward three quarts of thick pus were withdrawn from the chest by aspiration. Cough was constant and troublesome, and accompanied by abundant muco-purulent expectoration. He stated that at intervals he expectorated large amounts of fetid pus.

The patient, upon admission, was extremely emaciated and anæmic; cough was constant and troublesome; he suffered from hectic fever and profuse night-sweats. Upon physical examination, the signs of pneumothorax with fluid upon the left side were found present; the respiratory excursus was extremely limited; the lower intercostal spaces were obliterated. Above the level of the fourth rib the percussion was tympanitic. In this region there was amphoric respiration and typical response to the coin-test. The succussion-splash was easily developed. Below the level of the fourth rib there was flatness, which extended two fingers' breadth below the arch of the ribs, obliterating the semilunar space of Traube. There were signs of a large cavity at the right apex; the heart was displaced to the right, the impulse being distinct in the fourth and fifth intercostal spaces to the right of the sternum. The heart-sounds were most distinct at mid-sternum; and were well heard to the right of the sternum; there were no murmurs.

Upon inspection, there was distinct pulsation of the chest, synchronous with the heart's action, in the third, fourth, fifth, and sixth intercostal spaces on the left side, extending to the line of the anterior axillary fold. Pulsation, though not visible elsewhere, was perceived upon palpation at the arch of the ribs on the left side.

Some days after admission, about eight ounces of fetid pus were removed by aspiration. After this the pulsation became less marked. The patient declined operative interference, and owing to his wretched condition, it was not urged.

The patient left the hospital in December. Late in January he was readmitted, and died suddenly from pulmonary hemorrhage on February 25, 1893. An autopsy was not permitted.

With the assistance of Dr. A. A. Eshner, I have collected the notes of the following sixty-eight cases of pulsating pleural effusion.[1]

CASE 1. Baillou: Libri epidemiorum et ephemeridorum, Paris, 1640. Female. Pleurisy with enlargement of the side. Left side affected. Empyema necessitatis (?). One tumor. Diagnosis: aneurism. Treatment: cataplasms of flour and yolk of egg. Pus perforated lung, and tumor disappeared.

CASE 2. Pelletan (Keppler): Clinique Chirurgicale ou Mémoires et Observationes de Chirurgie Clinique, Paris, 1810. Male. After an acute illness. Left side affected. Empyema necessitatis. One tumor to left of sternum. Diagnosis: aneurism; patient considered tumor an abscess. Impulse of heart felt below right clavicle. Treatment: the patient punctured the tumor with a needle. Recovery. A student, wishing to satisfy himself that the heart had returned to its normal position, introduced a probe into the opening. The instrument slipped from his grasp into the cavity, whence it was removed at the end of three days by an incision through an intercostal space.

CASE 3. MacDonnell: Dublin Journal of Medical Science, March, 1844, xxv. p. 1. Female, aged 28. Acute pleurisy, two months. Left side affected. Empyema necessitatis. One tumor, precordial region. Diagnosis: strong diastolic pulsation, with expansile character. Treatment: rupture into œsophagus, and evacuated by vomiting. Death. Autopsy: Numerous cheesy tubercles in upper lobe of left lung; 4th and 6th ribs carious. Extensive abscess-cavity lined with a thick layer of coagulated fibrin. Lower lobe of left lung compressed.

CASE 4. MacDonnell: Dublin Journal of Medical Science, March, 1844, xxv. p. 1. Male. Chronic pleural effusion, three years. Left side affected. Empyema necessitatis. Two tumors: 1, region of apex of heart; 2, two inches from spinal column, between the 10th and 11th ribs. Diagnosis: energetic pulsation. Treatment: tumors punctured. Death six months later from pulmonary tuberculosis. The tumors were as large as Seville oranges, and evidently communicated with each other.

CASE 5. MacDonnell: Dublin Journal of Medical Science, March, 1844, xxv. p. 1. Male. Bronchitis followed by pneumonia, chronic pleural effusion, pneumothorax. Left side affected. Empyema necessitatis. Two tumors as large as eggs: 1, some inches above the nipple; 2, between the 10th and 11th ribs, two inches from the vertebral column. Treatment: repeated puncture. Death. Autopsy: Lung completely compressed and bound down by adhesions; infiltrated with tubercle; heart displaced to right and bound to right lung by adhesions; pericardium adherent; right lung sound.

CASE 6. Walshe: A Practical Treatise on the Diseases of the Lungs and Heart, 1851, p. 314. Left side affected. Intra-pleural. Subclavicular and mammary. Diagnosis: question of aneurism, absence of bruit, equality of pulses, absence of pressure-phenomena. Death. Heart displaced to right; aorta and pulmonary artery normal.

[1] These cases were originally arranged as a table, but are not so printed here for want of space.—J. C. W.

CASE 7. Walshe: Ibid. Case in all essential points like Case 6.

CASE 8. Stokes: The Diseases of the Heart and Aorta, Dublin, 1854. p. 607. Vast empyema, considerable displacement of heart to the right. Left side affected. Intra-pleural. Whole of left side. Diagnosis: heart displaced to right. Treatment: Paracentesis on three occasions.

CASE 9. Wintrich: Handbuch der speciellen Pathologie und Therapie, von R. Virchow, 1854, Bd. 5, pp. 259, 301. Left side affected. Probably empyema necessitatis. Between 4th and 6th ribs in front and to the left. Treatment: ruptured spontaneously. Pulsation ceased with evacuation of fluid. Pulsation ascribed to proximity of heart and great vessels.

CASE 10. Wintrich: Ibid. Case in all essential points like Case 9.

CASE 11. Asson (Keppler): Gior. Veneto di Scienze Med., Sept., 1885. Male, aged 21. Left side affected. Empyema necessitatis. One tumor below left nipple. Diagnosis: pulsation synchronous with heart-beat. Treatment: evacuation. Recovery.

CASE 12. Flint: Physical Exploration and Diagnosis of Diseases Affecting the Respiratory Organs, 1856, p. 581. Left side affected. Intra-pleural. Diagnosis: question of aneurism; absence of bruit, thrill, and pressure-phenomena; signs of pleural effusion.

CASE 13. Aran: Gaz. Méd. des Hôpitaux, June 9, 1858, t. iv. p. 91; also Bull. gén. de Thérap. Méd. et Chir., 1858, t. liv., livr. 12, p. 558. Female, aged 12. At the age of 6½ years bronchitis (with empyema (?)); Jan., 1858, left-sided pleurisy; failure to undergo resolution. Left side affected. Empyema necessitatis. One tumor between third and seventh interspaces to left of sternum. Diagnosis: pulsation with that of heart. Expiratory expansion and inspiratory retraction; tumor at first taken for an aneurism, then for diaphragmatic pleurisy. Treatment: punctured twice, spontaneous rupture, drainage, irrigation, injection of tincture of iodine. Patient was progressing toward recovery.

CASE 14. Rees: British Medical Journal, Aug. 21, 1858, p. 703. Male, aged 9. Left pleural effusion, eleven months. Left side affected. Empyema necessitatis. One tumor, three inches in diameter, to left of vertebral column above crest of ilium. Diagnosis: aneurism suspected; fluctuated and pulsated synchronously with the pulse-beat. Treatment: incision, escape of pus. Death. Left side of chest presented characteristic deformity of partially absorbed effusion of long standing; left lung compressed; fistulous tract; tuberculosis of left lung, pneumonia of right; tuberculosis of the meninges.

CASE 15. Heyfelder: Oester. Zeitschr. für praktische Heilkunde, Nov. 26, 1858, p. 860. Male, aged 46. Pain in right chest, extending to shoulder, for two months. Right side affected. Empyema necessitatis. One tumor 3 x 1½ inches; second interspace near the sternal border. Diagnosis: question of aneurism and of carcinoma; absence of bruit; puncture, pus. Treatment: incision, escape of pus, spontaneous opening. Recovery.

CASE 16. Heyfelder (Keppler). Male, aged 16. Left-sided pleural effusion of gradual development. Left side affected. Empyema necessitatis. Two tumors: 1, sixth interspace, close to sternum; 2, second interspace. Diagnosis: on auscultation, pulsation. Treatment: lower tumor opened subcutaneously; escape of pus; both tumors disappeared, also pulsation. At first improvement, ultimately death. Autopsy: Caries of 2d, 3d, 7th 8th, ribs; rupture of pleura; accumulation of pus between the layers of the chest-wall; left lung compressed, otherwise healthy.

CASE 17. Geigel (Keppler): Würzburg. med. Zeitsch., i. 2. Male, aged 57. Right-sided pneumonia eighteen months previously; ill nine days; weakness, cough, dyspnœa, fever. Right side affected. Empyema necessitatis. One tumor; right hypochondrium; from right border of sternum, following arch of ribs, a distance of 9 cm. toward the axillary line; upward almost as high as the nipple; divided into two, a smaller inner, and a larger outer. Death. Autopsy: Pericardial cavity contained five or six ounces of sero-purulent fluid; pleura greatly thickened; lined by false membrane; cavity contained from six to seven pounds of pus.

CASE 18. Baly: Lancet, Nov. 12, 1859, p. 482. Male. Pleurisy, twelve weeks; left-sided pleural effusion. Left side affected. Intra-pleural. Bulging of lower lateral aspect of left chest; prominent swelling of lower part of chest, with pulsation. Diagnosis: heart displaced to right. Treatment: tapped thrice. Pulsation appeared five months after the first tapping.

CASE 19. Wilks: Lancet, Nov. 12, 1859, p. 481. Male, aged 6. Right side affected. Empyema necessitatis. One tumor; seventh interspace, right side of chest anteriorly. Treatment: tapped; nearly one pint of pus; spontaneous evacuation. Discharge continued.

CASE 20. Chambers (reported by Ash): Lancet, May 31, 1862, p. 573. Male, aged 49. Left-sided pleurisy, eight weeks. Left side affected. Intra-pleural and empyema necessitatis. Indistinct undulatory motion in interspaces on left side below mammary line; slight swelling in fifth interspace. Diagnosis: synchronous with pulse-beat. Treatment: leeches, poultice; ruptured spontaneously. Recovery; well two years later. Pneumothorax and subcutaneous emphysema developed.

CASE 21. Chambers: Ibid. Diagnosis: resembled aneurism. Recovery.

CASE 22. Willshire (reported by Chandler): Lancet, May 31, 1862, p. 573. Male, aged 35. Blow upon left side half a year before. Left side affected. Empyema necessitatis. One tumor; eighth interspace at junction of diaphragm and ribs; transversely oval; size of hen's egg. Diagnosis: pulsation synchronous with heart-beat; simulated aneurism; absence of thrill and bruit. Treatment: incision, evacuation. Recovery. Chest flattened, spine curved.

CASE 23. Chvostek: Wochenbl. der Zeitschr. der k. k. Gesellschaft der Aerzte Wien. Beiträge zu den medicin. Jahrb., Jahrg. xxi., 1865, No. 7, p. 49 et seq. Male, aged 27. Acute empyema about one month. Left side affected. Empyema necessitatis. Three tumors: 1, retro-axillary region; 2, fourth interspace between sternum and nipple; 3, in axillary space near fifth interspace. Treatment: incision, evacuation. Death. Posterior tumor did not pulsate, anterior one synchronously with pulse. Autopsy: Several ribs denuded and eroded; intercostal muscles much altered; left pleural cavity contained much yellowish, flocculent, fetid fluid; pleura thickened; lung compressed; pericardium adherent; heart at mid-sternum.

CASE 24. Chvostek: Ibid. Male, aged 23. Left-sided pneumonia, followed in fifty-four days by pleural effusion. Left side affected. Empyema necessitatis. One tumor; fifth interspace. Diagnosis: synchronous with heart-beat. Death. Autopsy: collection of pus beneath pectoralis major; left thoracic cavity filled with flaky, yellow lymph; right lung compressed and displaced upward and forward; remains of pneumonia at apex; recent pericardial adhesions.

CASE 25. Chvostek: Ibid. Male, aged 25. Left pleuro-pneumonia, one month. Left side affected. Empyema necessitatis. One tumor; fourth interspace near nipple. Diagnosis: Pulsated synchronously with heart. Treatment: repeated incision; spontaneous opening.

CASE 26. Lesage: Gaz. des Hôpitaux, October 31, 1865, p. 511. Female, aged 38. Left side affected. Empyema necessitatis. Recurrent abscess-formation; tumor between third and fourth interspaces on left at sternal junction; hemispherical. Diagnosis: aneurism excluded, empyéme pulsatile a repetition. Treatment: spontaneous rupture. Deformity of chest.

CASE 27. Reyher: Berliner klin. Woch., 1868, p. 426. Empyema necessitatis (?). Diagnosis: Pulsating periosteal abscess.

CASE 28. Courbon (reported by Le Double): Gaz. des Hôpitaux, May 24, 1870, p. 237. Female, aged 24. Ill four years, dyspnœa, palpitation; tumor, two months. Left side affected. Empyema necessitatis. One tumor, lumbar region, 14 x 11 cm. Diagnosis: regarded as aneurism; absence of thrill and bruit; heart displaced to right. Treatment: opened spontaneously. Escape of pus; disappearance of pulsation.

CASE 29. Toft: Bidrag til Kundskab om Empyem, Nord. med. Arkiv, Bd. 3, 1870, Virchow-Hirsch, Jahresbuch, 1871, Bd. ii, p. 116 (Keppler). Left side affected. Empyema necessitatis.

CASE 30. Toft: Ibid. Left side affected. Empyema necessitatis.

CASE 31. Toft: Ibid. Left side affected. Intra-pleural. In the three cases of Toft the pulsation was ascribed to the impulse of the current of blood as it was forced through the fixed or displaced aorta.

CASE 32. Müller: Berliner klin. Wochenschr., Jan. 22, 1872, p. 37. Male, aged 21. Left pleuro-pneumonia six weeks; one year previously painful affection of left chest with cough. Tumor several months. Left side affected. Empyema necessitatis. One tumor; from third to sixth interspace, from sternum to axilla. Diagnosis: Aneurism considered; absence of bruit and thrill. Treatment: incision in fifth interspace; evacuated 300 c.cm. pus. Recovery.

CASE 33. Plagge: Beitrag zur Kenntniss der pulsirenden Thoraxgeschwüstem, Memorabilien, 1872, No. 11. Male, aged 21. Left-sided pleuro-pneumonia, six weeks. Left side affected. Empyema necessitatis. One tumor; upper part of chest anteriorly, below second rib, from border of sternum to nipple line; continuity of second and third ribs interrupted. Treatment: incision, evacuated thick pus. Recovery. The occurrence of pneumothorax was immediately followed by the disappearance of the tumor.

CASE 34. Traube: Berliner klin. Wochenschr., Feb. 12, 1872, p. 77; also Verhandl. der Berliner med. Gesellsch, ii. p. 49 et seq. Male, aged 24. Acute empyema, two months. Left side affected. Intra-pleural. Second to sixth interspaces, 1¾ to 3⅝ inches; from 1⅞ to 3⅞ inches from middle line Diagnosis: systolic pulsation. Death. Autopsy: Massive purulent effusion; lung compressed and adherent; costal pleura destroyed throughout considerable extent, and in particular opposite the seat of pulsation during life; pericardium thickened; contained four ounces of brownish fluid; right lung slightly adherent, otherwise normal.

CASE 35. Traube: Ibid. Left side affected. Intra-pleural. Diagnosis: systolic pulsation.

CASE 36. Fräntzel: Ziemssen's Cyclopedia, Leipzig, 1875, Bd. iv. 2. p. 351; Amer. ed., iv. p. 639. Left-sided purulent pleurisy. Left side affected. Intra-pleural. Fifth and sixth interspaces between mammillary and axillary lines; extent moderate. Treatment: puncture followed by incision. A considerable purulent effusion associated with pericarditis.

CASE 37. Topham: Lancet, May 25, 1878, p. 756. Female, aged 21. Six months after a blow, pain in the side. Left side affected. Empyema necessitatis. One tumor between third and fourth ribs at sternal border. Diagnosis: the tumor was regarded as an abscess, but it so closely resembled an aneurism that the patient was kept in bed three years. Treatment: spontaneous rupture; escape of much caseous matter. Fistula persisted long; patient resumed avocation.

CASE 38. Henry: Proceedings Phila. County Medical Society, 1881, vol. iii. p. 85. Female, aged 30. Left side affected. Empyema necessitatis. Three tumors: 1, size of half a large orange, in mammary region; 2, smaller, acuminated, on antero-inferior aspect of chest; 3, largest, on postero-inferior aspect; vertical diameter four inches. Treatment: pus withdrawn with syringe from smallest tumor; tumor over heart contained air; aspiration, later drainage. Patient well a year after operation.

CASE 39. Brünniche: Virchow-Hirsch Jahrb., 1882, Bd. ii. p. 146. Pleurisy. Left side affected. Empyema necessitatis. One tumor below angle of scapula. Treatment: exploratory puncture. A large, fluctuating, subcutaneous tumor; in the tenth interspace an opening could be felt that communicated with the pleural cavity.

CASE 40. Comby: Archives générales de Médecine, Dec., 1883, p. 689. Female, aged 28. Pulmonary tuberculosis, two years; latent, ancient, left-sided pleurisy. Left side affected. Intra-pleural. Posterior and median portions of 9th, 10th, 11th interspaces bulging, prominent fluctuating, pulsatile. Diagnosis: aneurism of thoracic aorta considered. Treatment: exploratory puncture, aspiration, evacuation of pus. Pulsation grew less and disappeared; finally death. Autopsy: Tuberculosis of both lungs; heart displaced to right; fetid gas and flaky pus in left pleura; no false membrane; left lung scarcely discernible; pericardium contained a little fluid, adherent to left lung; on surface of left lung two perforations communicating with bronchi; right pleura adherent to pericardium; mediastinum displaced; liver displaced.

CASE 41. Comby: Arch. gén. de Méd., Dec., 1883, p. 691. Male, aged 24. Bronchitis three years previously, followed by hæmoptysis; oppression of chest and pain in left side, two years. Left side affected. Intra-pleural. In precordium gentle pulsation; all of the interspaces on the left seem widened and bulging anteriorly and posteriorly; synchronous with heart-beat; most marked posteriorly between seventh and tenth interspaces. Diagnosis: heart-beat between second and fifth interspaces on right. Treatment: Thoracentesis. More than three litres of pus withdrawn; pulsation diminished and disappeared; pneumothorax developed; pulsation reappeared at lower part of axilla.

CASE 42. Comby: Arch. gén. de Méd., Dec., 1883, p. 694. Male, aged 35. Ill three months; pain in the chest one and a half months; pleural effusion; thoracentesis. Left side affected. Intra-pleural. Pulsation of the chest-wall below and behind. Diagnosis: heart displaced to right. Treatment: puncture. Death in two hours. Evacuated two litres of pus. Autopsy: Heart displaced to right; pericardium contained a little serous fluid; left pleura contained two litres of pus; left lung displaced toward mediastinum and adherent to left face of pericardium; lung sclerotic; apex and posterior border adherent; two caseous nodules at summit of right lung.

CASE 43. Comby: Arch. gén. de Méd, Dec., 1883, p. 695 (case of Duguet). Male, aged 36. Pleurisy one year previously; ill one month; effusion eighteen days; tuberculous broncho-laryngitis. Left side affected. Intra-pleural. Inferior and lateral half of left chest. Diagnosis: synchronous with heart-beat. Treatment: thoracentesis. Death. 3½ litres offensive purulent

liquid removed, followed in two weeks by pulsation; signs of pneumothorax; liver displaced; heart displaced.

CASE 44. Yeo: Lancet, Feb. 23, 1884, p. 331. Male, aged 41. Left-sided pneumonia eight months previously. Left side affected. Empyema necessitatis. One tumor between fourth and fifth ribs, a little external to nipple, 2½ x 1 inch, projecting ½ inch above surface. Diagnosis: synchronous with cardiac pulsation; cardiac impulse in epigastrium to right of lower half of sternum. Treatment: exploratory puncture, incision, antiseptic dressing, drainage. Left hospital six weeks after operation. Sixty ounces of pus removed.

CASE 45. Pel: Berliner klin. Wochenschr., Feb. 25, 1884, p. 113. Male, aged 32. Ill four weeks; chill, chest-pains (left), fever, cough, expectoration; empyema; pus evacuated, eighth intercostal space, posterior scapular region; irrigation. Left side affected. Intra-pleural. Posteriorly. Diagnosis of purulent pericarditis made, but found incorrect upon post-mortem examination. Treatment: pus evacuated; irrigation. Death. Two distinct encapsulated left-sided empyemata; pus ejected in a stream synchronous with the action of the heart. The heart lay close to the inner border of the anterior collection of pus, from which it was separated only by a layer of pericardium.

CASE 46. Dillingham: Medical Record, March 8, 1884, p. 263. Male, aged 26. Ill ten months; pain in chest, cough, expectoration, pleural effusion, succussion-phenomena. Left side affected. Intra-pleural. Bulging of left side of chest, with distinct pulsation. Diagnosis: aneurism considered, but excluded. Treatment: repeated aspiration; free incision. Death. Succussion-phenomena; pulsation appeared after fifth removal of pus. Probe arrested by pulsating body; sac perforated; 156 ounces of pus evacuated; irrigation. Left pleural cavity contained blood-clots; walls covered with pyogenic membrane; lung atelectatic, slate-colored; indurated.

CASE 47. Féréol: Prot. de l'Acad. de Méd., No. 7, Virchow-Hirsch, Jahresb., 1884, Bd. ii. p. 155. Male, aged 2. July, 1882, left-sided pleurisy, aspiration, recovery. Oct. 27, 1882, left-sided pleural effusion, with gas. Left side affected. Intra-pleural. General pulsation of whole of left chest, most marked posteriorly and inferiorly. Diagnosis: synchronous with heart-beat; apex-beat at right nipple. Treatment: aspiration, resection. Recovery. 2½ litres laudable pus removed; pulsation disappeared; pus reaccumulated, symptoms returned. Féréol maintains that the presence of gas is essential to the development of pulsation, without communication with a bronchus and under greater pressure than that of the atmosphere.

CASE 48. Broadbent: Lancet, May 31, 1884, p. 971. Female, aged 19. Ill two months. Left side affected. Intra-pleural. Pulsation at usual site of apex, in fifth interspace, along last costal cartilage to ensiform cartilage; also in tenth interspace from near spine to beyond angle of ribs. Diagnosis: heart displaced to right of sternum; pulsation in cardiac region supposed to be due to aneurism or malignant tumor, probably the latter. Death. Autopsy: Effusion; heart hypertrophied, adherent to pericardium; pericardium adherent to central tendon of diaphragm and to chest-wall; pulsation ascribed to traction upon pericardial adhesions.

CASE 49. Ross: Canada Med. and Surg. Journ., May, 1885, p. 606. Male, aged 37 Pneumonia five years previously; abed three months; five days after a wetting, left-sided, pleural effusion. Left side affected. Empyema necessitatis(?). One tumor, second and third interspaces, in front. Diagnosis: synchronous with heart-beat; simulated aneurism. Treatment: spontaneous evacuation. Recovery; left hospital ten weeks after onset. Five weeks after onset of illness, after severe attack of coughing, at least a pint of thick, creamy, odorless pus ejected; cough continued for a few days, with the expectoration of pus; pulsating tumor had disappeared.

CASE 50. Codivilli: Thesis, Bologna, 1886. Male, aged 21. Sept., 1884, chill, fever, headache, stupor. Oct. 17, 1885, left-sided pleural effusion. Left side affected. Empyema necessitatis. One tumor on left side posteriorly and inferiorly, corresponding with last two ribs, became as large as a fist. Diagnosis: synchronous with the diastole of the great vessels; heart displaced to right. Treatment: exploratory puncture; thoracentesis repeated; spontaneous rupture; irrigation; Estlander's operation. Improvement.

CASE 51. Borgiotti (Case of Bernabei: Clinica Medica in Bolletino della Soc. Cult. delle Scienze, Feb., 1886): Bolletino della Societa Culturi delle Scienze. Siena, 1887, pp. 91-95. Male, aged 39. Right-sided pleurisy, two months; pneumothorax; thoracentesis thirty days previously; empyema, twenty days. Right side affected. Intra-pleural. Whole left wall of chest shaken by pulsation; the entire anterior aspect of the right chest, especially between the third and sixth ribs. Diagnosis: apex-beat in left fifth interspace, 1 cm. beyond nipple line.

Treatment: repeated thoracentesis. Patient at work after nine months. During one night the patient expectorated nearly a pint of pus; in the morning the pulsation was sensibly diminished. Pus reaccumulated; pulsation returned.

CASE 52. Cammareri: Gazzetta degli Ospitali, 1886, No. 97, p. 772; No. 98, Dec. 8, p. 780. Male, aged 28. Seven weeks previously chills, fever in left chest, dyspnœa. Left side affected. Empyema necessitatis. One tumor as large as a lemon between inferior margin of second rib, superior margin of seventh rib, and left margin of sternum. Diagnosis: apex-beat to right of sternum. Treatment: spontaneous rupture; escape of pus. Death from intercurrent affection. Autopsy: Parietal pleura thickened, covered with pus; cavity contained six ounces pus, divided by false membrane into two compartments, lung above, pus below; changes in ribs, cartilages, and soft parts.

CASE 53. Keppler: Deutsches Archiv für klin. Medicin, 1887, Bd. xli. p. 225 (Case of Eichhorst). Male, aged 14. Ill fourteen days; soon right pleural effusion; history of injury possible, but positive evidence wanting. Right side affected. Intra-pleural and empyema necessitatis. Antero-lateral aspect of left chest as high as the third rib. One tumor; on level with seventh rib, between anterior axillary line and nipple line. Diagnosis: synchronous with heart-beat. Treatment: aspiration repeated, exploratory puncture, resection of rib. Recovery. Evacuated nearly half a pint of serum; after two weeks tumor formed; evacuated more than a pint of pus; fistula persisted; pus reaccumulated.

CASE 54. Rummo: Riforma Medica, 1888, p. 1316 et seq. (Martinez). Male, aged 21. April, 1884, cough, expectoration, shortness of breath, blood-streaked sputum, feverishness. May, 1884, chilled while overheated; severe pain in left chest; chest enlarged for twenty days Left side affected. Intra-pleural. Second, third, and fourth interspaces from sternum to anterior axillary line. Treatment: exploratory puncture; aspiration repeated. Death. Hemorrhagic serum, no tubercle-bacilli found. Three pints of bloody serum removed. Symptoms returned.

CASE 55. Rummo. Male, aged 23. July, 1887, acute, intense pain in left chest, chilliness, feverishness; soon pulsation to right of sternum; cough, muco-purulent expectoration. Left side affected. Intra-pleural. Between sternum and spinal column from level of clavicle to level of spine of scapula. Diagnosis: resembled aneurism. Treatment: exploratory puncture. Evacuated nearly seven pints of pus; pulsation ceased. Symptoms returned, without pulsation; four pints of pus removed.

CASE 56. Rummo. Male, aged 25. Nov., 1887, pain in left chest, oppression, shortness of breath, cough, muco-purulent expectoration. Left side affected. Intra-pleural. At base of left chest, between posterior axillary line and spinal column. Treatment: aspiration. Improvement. Nearly five pints of pus evacuated; pulsation disappeared.

CASE 57. Osler: Transactions Association of American Physicians, 1888, iii. p. 330. Male, aged 23. Feb. 23d, strained back in lifting; pain in left side; effusion. March 6th, fifty ounces serum aspirated. March 9th, two quarts turbid serum removed; pyo-pneumothorax. Left side affected. Intra-pleural. Fourth, fifth, sixth interspaces in mid-axillary line. Treatment: aspiration repeated. Recovery. Removed fifty ounces clear serum; two quarts slightly turbid serum; pulsation observed; three pints pus evacuated.

CASE 58. Janeway (cited by Osler): Trans. Assoc. Amer. Phys., 1888 (personal communication). Left side affected. Empyema necessitatis. One tumor, left second interspace. Pulsated when patient stood erect; sac filled with air when the patient assumed recumbent posture.

CASE 59. Millard: Gaz. hebd. de Méd. et de Chir., July 12, 1889, p. 447. Male, aged 36. Bronchitis and pulmonary congestion, twelve years. Dec., 1885, cough. May, 1887, left-sided pleurisy, pneumothorax, recovery. Dec., 1887, dyspnœa and signs of pneumothorax. Left side affected. Empyema necessitatis. One tumor below and behind, to left of vertebral column; attained the volume of an orange. Diagnosis: one physician diagnosticated aneurism. Treatment: thoracentesis; five additional punctures; injection of from 80 to 115 grms. tincture of iodine; 1250 grms. pus removed; 115 grms. tincture of iodine injected; resection of rib, lavage; death. 3½ litres creamy, odorless pus evacuated; pulsation disappeared; fluid reaccumulated. From 1300 to 1500 grms. of pus removed. Reappearance of signs of pneumothorax; tumor of back began to reform, but not to pulsate.

CASE 60. Wilson: Proceedings Philadelphia County Medical Society, 1889, x. p. 152. Male, aged 20. Three years previously chest trouble (four weeks). Six weeks previously twisted left side in lifting; pain; dyspnœa; cough; tapped thrice in nine days; much fluid withdrawn, at

first clear, later turbid. Left side affected. Intra-pleural. Whole left chest, anteriorly and laterally as far as anterior axillary line; most distinct in second and third interspaces to left of nipple line. Diagnosis: heart displaced to right. Treatment: aspiration, resection of ribs. Patient lost sight of. Three pints foul-smelling, greenish-yellow pus removed. Accumulation returned, with pulsation; four pints pus evacuated; drainage-tube; antiseptic dressing; bell-sound; pyo-pneumothorax.

CASE 61. Monari: Gazzetta degli Ospitali, Aug. 6, 1890, No. 63, p. 448. Male, aged 31. Oct., 1888, chill, fever, pain in left side, cough; pneumonia. In convalescence pain returned. Pleural effusion formed; exploration; pus. Left side affected. Empyema necessitatis. One tumor, size of apple, inferior and posterior aspect of left chest. Treatment: pleurotomy, irrigation. Patient resumed avocation in six weeks.

CASE 62. Light: Lancet, London, Sept. 26, 1891, ii. p. 705. Aged 3. Cough, dyspnœa, vomiting five weeks; left-sided pneumonia. Left side affected. Empyema necessitatis. Two tumors, one in precordium, the other in the eighth interspace, in mid-axillary line; the second pulsated. Diagnosis: Heart displaced to right of sternum. Treatment: exploratory puncture, pleurotomy, drainage-tube, antiseptic dressing. Death. 25 ounces sweet pus evacuated. Autopsy: heart appeared to be in normal position; right lung expanded, left just visible, small, collapsed, lay against mediastinum; remainder of pleural cavity empty, no pus visible, pleura thickened, covered with pyogenic membrane, adherent to thickened pericardium; right pleura coated with recent lymph; cavity contained two ounces purulent fluid; peritoneum presented signs of recent inflammation; cavity contained four ounces purulent fluid; no evidence of communication between pleural and peritoneal cavities.

CASE 63. Light: Ibid. Male, aged 20. Thirteen weeks previously, lassitude, anorexia, pleurisy(?); in four weeks aspiration of fluid "turning to matter." Left side affected. Treatment: pleurotomy. Death soon after operation. 80 ounces sweet pus evacuated. Autopsy: External tumors contained pus; communicated with pleural cavity by fistulæ; heart to right of mid-sternum; twisted on its axis; pericardium contained eight ounces of clear serum; left surface adherent to left pleura; left pleura thickened; covered with pyogenic membrane; left lung compressed to size of hand, pushed toward mediastinum and vertebral column.

CASE 64. Light: Ibid. Male, aged 4. Jan., 1890, pertussis; April, 1890, pain in left side. Left side affected. Empyema necessitatis. Two tumors: 1, 5th, 6th, 7th interspaces and ribs between nipple and mid-axillary lines; 2, 8th, 9th, 10th ribs and spaces in a line with the angle of the scapula. Diagnosis: synchronous with cardiac impulse; heart displaced to right of mid-sternum. Treatment: pleurotomy, drainage-tube, antiseptic dressing. Recovery. 30 ounces pus evacuated; retraction of the left side; some curvature of the spine.

CASE 65. Shattuck: International Clinics, Jan., 1892, p. 87. Female. Pneumonia left lower lobe, twenty-two days. Left side affected. Intra-pleural. Not well defined. Diagnosis: aneurism and tumor excluded; concluded to be pleural effusion or pericardial effusion, or both. Treatment: aspiration, incision. Recovery. 8 ounces thick pus evacuated.

CASE 66. Watkins: Lancet, Jan. 21, 1893, p. 133. Female, aged 18. For six years dry, hacking cough; four days previously muscular strain, Left side affected. Intra-pleural. From 3d to 6th interspace in mid-axillary line. Diagnosis: heart displaced to right. Treatment: exploratory puncture, aspiration, drainage-tube. Improved; dismissed. Clear fluid. 36 ounces fluid; reaccumulated; 40 ounces turbid fluid removed; pulsation; thought to have been pneumothorax.

CASE 67. Wilson: Trans. Assoc. Amer. Phys., May–June, 1893. Male, aged 22. Left-sided pneumonia five weeks previously, followed by pleural pain and effusion; emaciation, anæmia, mucous expectoration. Left side affected. Intra-pleural. From second interspace to base of chest to mid-axillary line. Diagnosis: heart displaced to right. Treatment: aspiration. Recovery. 13 ounces light-colored, creamy pus, then 80 ounces pus; pulsation disappeared and did not return. Fluid reaccumulated; pus removed and replaced by normal saline solution.

CASE 68. Wilson: Ibid. Male, aged 21. Ill two years, influenza, failure of health, cough, fever, sweats, hæmoptysis. Aug., 1892, left-sided pleural effusion. Left side affected. Intra-pleural. 3d, 4th, 5th, 6th interspaces to anterior axillary line. Diagnosis: heart displaced to right. Treatment: aspiration. Death. 8 ounces pus; pulsation less.

Of the 68 cases, the sex is stated in 52. Of these, 41 were males; 11 females.

The age is given in 47 cases. It varied from 2 to 57 years.

The cases were distributed among the quinquennial periods as follows: Up to 5 years there were 3; between 6 and 10, 2; between 11 and 15, 2; between 16 and 20, 3; between 21 and 25, 16; between 26 and 30, 8; between 31 and 35, 4; between 36 and 40, 5; between 41 and 45, 1; between 46 and 50, 2; between 51 and 60, 1.

The side affected is named in 66 cases. Of these, the left was affected in 61; the right, in 5.

The character of the lesion is stated in 67 cases; of these, 37 were of the nature of empyema necessitatis; 28 were intra-pleural. In 2 cases both varieties of pulsation were present.

Of 5 cases in which the right side was affected, 3 were of the nature of empyema necessitatis; 1 was intra-pleural; and in 1 both varieties were present.

In 33 of the cases of empyema necessitatis the number of tumors is stated. In 28 there was 1; in 5 there were 2; in 2 there were 3.

The outcome is stated with more or less definiteness in 46 cases. Of this number, recovery took place in 24; death in 22.

Of the total number of cases, 1 was reported in 1640; 1 in 1810; 3 between 1840 and 1849; 14 between 1850 and 1859; 8 between 1860 and 1869; 10 between 1870 and 1879; 23 between 1880 and 1889; 8 since 1890.

The pulsations are synchronous with the ventricular systole. As a rule, they may be detected alike upon inspection and palpation. Sometimes they are not visible, but may be recognized by palpation only. When intra-pleural, the pulsation may be limited to two or three intercostal spaces. More commonly it occupies the greater part of the anterior aspect of the thorax as far to the left as the anterior axillary line. In some cases it has occurred posteriorly, and, in a few instances, as in the cases reported by Rees,[1] by Courbon,[2] and in one referred to by J. M. Barton, a pulsating empyema necessitatis existed in the left lumbar region. Frequently the pulsation is only of moderate force, requiring some attention for its recognition. In some of the cases, however, it has been forcible.

[1] British Medical Journal, Aug. 21, 1858, p. 703.
[2] Gazette des Hôpitaux, May 24, 1870, p. 237.

In the majority of cases the left side was affected. Comby, writing in 1889, said: "Il faut ajouter que les pleurésies pulsatiles sont toujours situées à gauche; on trouverait peut-être une exception à cette règle, on aurait de la peine à en trouver deux."

Of the 66 cases in which the side is designated, the left was affected in 61 and the right in 5—8.2 per cent.

Most of the cases are reported as cases of pulsating empyema. In 41 cases, in which the notes refer to the character of the pleural contents, it is said that in 37 pus was present; in 1, yellowish fetid fluid; in 1, caseous matter; in 1, bloody serum; in 1, turbid fluid. In the remaining 27 cases nothing has been noted of the character of the pleural contents.

Pulsating empyema has been mistaken for aneurism of the aorta. Only in exceptional cases does the differential diagnosis between these two conditions present serious difficulty. Aneurism of the aorta bears a definite relation to the central long axis of the chest; its invasion of regions of normally clear percussion is circumscribed; it is usually the seat of murmurs or other sounds synchronous with the rhythm of the heart. The signs of pulsating empyema, whether intra-thoracic or an empyema necessitatis, are, on the other hand, usually upon the left side and at a distance from the median line; the percussion-dulness is uniformly at the base of the chest and extended, and murmurs are not present. Empyema necessitatis is influenced by pressure and by the respiratory movement in the chest-wall; aneurism is not.

Difficulty as to the differential diagnosis between pulsatile empyema and thoracic aneurism can only arise in the case of an encysted empyema in close relation with the heart.

The anatomical conditions underlying pulsation in pleural effusions are: First, some degree of paresis of the intercostal muscles, such as occurs only in large pleural effusions usually of long standing; second, local necrosis and perforation of the parietal pleura (empyema necessitatis); in both these conditions there is relative weakening of the wall of the chest; third, pneumothorax, either latent or manifest. This condition has been observed in a majority of the cases; in a small number it has been apparently absent. In Case II. of my series it was carefully sought for, but not found. Fourth, an atelectatic condition of the lung in whole or in part, the left lung being in relation with and adherent to the pericardium.

In case I. of my series the persistence of the pulsation in the upper intercostal spaces after Estlander's operation had been performed is to be explained by the fact that a strip of adherent and compressed lung extended from the pericardium to the point in question.

Numerous theories have been advanced in explanation of the phenomenon of pulsation in pleural effusions:

1. That of Traube, which attributes the pulsation to the condition of the heart and the pericardium; but cardiac hypertrophy and pericardial adhesions, far from being the rule, have been the rare exception, though pleuro-pericardial adhesions, as in all general pleurisies, have been noted.

2. A second theory attributes the conduction of the pulsation to the compressed and carnified lung; but as compression and carnification, with pleuro-pericardial adhesion, take place in all massive effusions, this condition cannot be invoked to explain the occurrence of a phenomenon so rare as that of pleural pulsation. This was the theory first advanced, but afterward withdrawn, by Comby.

3. The theory of Féréol assigns the pulsation to a pneumothorax of moderate extent, which may often be latent. The pulsation is here attributed to the transmission of the cardiac impulse through the confined air in the manner in which compression-waves are transmitted through the rubber apparatus of the cardiograph and other similar instruments. That this theory is insufficient, becomes manifest from the fact that in the majority of the cases of effusion with pneumothorax, pulsation is absent, and in certain of the cases, notably in Case II. of my series, pneumothorax, as shown by the history of the case and by most careful search, did not exist.

4. The fourth theory attributes the pulsation to a variety of associated pathological conditions: paresis of the intercostal muscles; intrapleural pressure; the energy of the heart's action. But weakening of the chest-wall and enfeeblement of the intercostal muscles are common conditions in old empyemata; forcible action of the heart, far from being the rule in pulsating empyemata, is the exception, and as to intra-pleural tension it is variable in pulsating effusions, and occasionally absent altogether.

To sum up: no one of the theories hitherto advanced is adequate to account for the rare phenomenon of pulsation in pleural effusion. We must await facts not yet brought to light to fully explain its

mechanism. Among the conditions not hitherto noted which favor pulsation are (*a*) strands of atelectatic lung-tissue, reaching from pleuro-pericardial adhesions at one extremity by way of pleural adhesions at the other to the surface of the chest, and thus acting as conductors of the cardiac impulse, and (*b*) the elasticity of that part of the wall of the thoracic cavity on the left side, formed by the diaphragm in its relation to the fundus of the stomach. The latter condition, together with the convexity of the left wall of the heart in systolic tension and the almost synchronous diastolic tension of the aorta of the left side of the chest, as pointed out by Toft and Wintrich, serves to explain the greater frequency of pulsation in left-sided effusion.

DISCUSSION.

DR. OSLER: I wish to speak of a case of pulsating pleural effusion that has many interesting features. The patient was a young woman, who was transferred to my ward from the gynecological ward, where she had laparotomy performed for supposed abdominal tumor, which proved to be a movable spleen. She had practically recovered from the laparotomy, but had had fever for several days, and was transferred because the resident on the gynecological side had detected signs of pleurisy. On examination, there was presented a very remarkable condition of the chest on the left side, and for a moment I could not think what it possibly could be. From the sternum to the axillary fold on the left side, and from the clavicle to the fourth rib, there was a pulsation quite similar to, and quite as forcible as, a diffused aneurismal pulsation limited to this region. There was no pulsation perceptible at the base or in the lower axillary region. The fluid was drawn off by an aspirator, and the pulsation disappeared. It was a serous exudate. Curiously enough, in both of the cases which have come under my observation, the exudate was serous. In this case the fluid did not again accumulate, and the patient made a rapid convalescence. She returned a week or two after her discharge from the hospital, with a very large abdominal tumor distending the lower costal border, and occupying nearly one-half of the left side. This was incised by Dr. Halsted, and proved to be a strangulated and necrotic spleen. For weeks large masses of necrotic spleen tissue came away, but she ultimately made a very good recovery.

DR. MASON: I have listened with very great interest to Dr. Wilson's valuable addition to our knowledge of a subject in which I have had no personal experience. It must be an extremely rare thing that three cases of this affection should come under the observation of one physician in such a short time.

DR. LOOMIS: There is incidentally a very interesting subject brought up in connection with this subject, namely, the treatment of empyema. If I understand Dr. Wilson, in two instances he introduced a large trocar, and through that introduced a flexible tube. It seems to me that if there is one thing more fully settled by experience than another in regard to the management of these cases, it is that the earlier a free and extensive opening is made the better, and if the case is of long-standing, the sooner exsection of one or more ribs is done the better for the patient; the cavity should be treated by packing rather than by other methods. This, I think, has been pretty well established in the last year or two by those experienced in the management of these cases. I certainly should hesitate to make a small opening and introduce merely a tube for drainage, however low I might be able to enter the pleural cavity.

DR. FITZ: Possibly the case which Dr. Wilson has recorded is one which was treated before the method of free opening was as extensively employed as at present. The custom in regard to packing, it seems to me, may also be considered as capable of improvement by the introduction of merely enough gauze for drainage, without any extensive packing.

DR. OSLER: I have been very much impressed by the good results which my colleague, Dr. Halsted, has obtained by very free opening and packing, for a time at least, with gauze. The results which he has had in the cases of empyema transferred to his wards from the medical side in the past three years have been uniformly good. I do not remember at this moment a fatal case following operation for simple empyema.

DR. WILSON: I have been impressed with the admirable results following the surgical treatment of empyema. My attention has not been fully called to the importance of packing what is really an abscess cavity under these circumstances. One of my cases was not treated at all, and the other two were treated at a period when the line of treatment just suggested had scarcely been so fully formulated as at present. The first case was treated in 1889. An attempt was made to manage the case by a drainage-tube, and that failing, an operation was performed. The patient made a partial recovery and was lost sight of. The other case was treated in 1891, early in the year, and after an ineffectual attempt to manage it by the method of Lewaschew it was treated by a drainage-tube, and made an excellent recovery in a short time. The tube was introduced on the 16th of April, and on the 12th of May the tube was withdrawn, and the patient made a complete recovery, with an expanded lung, in the further course of about a fortnight. It seems to me that we cannot be too dogmatic in our generalizations in regard to the management of these cases. From what is now known regarding the etiology of different forms of empyema, it is probable that there is a very large class of cases that can be perfectly well managed by means of evacuation through a relatively small opening, and without submitting the patient to a surgical operation, which requires a good

deal of cutting, and which demands the administration of ether or other anæsthetic not always readily assented to by either the patient or his family, and not without some misgiving on the part of the physician when he considers that the function of the lung and the circulation of the chest are largely hampered by mechanical pressure.

Speaking of the different forms of empyema from the standpoint of their etiology, I refer to their bacteriological nature. It is now generally admitted by those who have carefully looked into the subject, that there is at least one form of pleural effusion in which the tendency to recovery under moderately favorable circumstances is very great. I refer to that form, common in children and not uncommon in early adult life, which is due to infection by the pneumococcus, a form of empyema which gave rise to much confusion and uncertainty in regard to treatment at an earlier period. This form of empyema tends to recovery under any reasonable kind of management. After evacuation the pus in many of the cases does not tend to return, and the mortality is probably not much greater than 2 per cent. I think it justifiable in such cases to advocate simple drainage by a tube introduced through a trocar.

DR. LOOMIS: I have instituted a series of experiments on the development of pleurisy by different microbes introduced into the pleural cavity. These experiments have been going on for about a year. There is a very great difference in the character of the pleurisy produced by the different microbes. The pneumococcus gives pus in the largest quantity, and the most rapidly developed. I would like to refer to one case, in a child one and a half years old, in which the cavity filled up and pushed the heart well over to the right in about forty-eight hours. It was first aspirated with but little relief. Afterward a portion of one of the ribs was excised, and a free opening made, and from that time recovery went on very rapidly. This is the youngest subject that I have seen in which a portion of the rib was excised.

SUBPHRENIC ABSCESS, WITH SPECIAL REFERENCE TO THOSE CASES WHICH SIMULATE PYO-PNEUMOTHORAX.

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THE systematic treatises on medicine and surgery make little mention of abscesses of the sub-diaphragmatic region, from the fact that they are not dependent on diseases of any one organ, but are rare sequels of various affections, and give rise to symptoms and physical signs which are hard to classify for purposes of diagnostic differentiation. But within recent years, from the evidence of post-mortem examinations, where such lesions had been unsuspected during life and where their symptoms had been misinterpreted, as well as from the gradual refinement in the accuracy of physical diagnosis, single cases, or small groups of cases, of this description have been oftener reported in medical journals, so that it is now easy, through analysis of these observations, to recognize the varied etiology of these grave conditions, and, from a knowledge of their causation, to see more clearly their clinical import and therapeutic indications.

While collections of pus within the thorax may usually be detected with a fair degree of certainty, it is not so when they are seated high up under the arch of the diaphragm, circumscribed by peritoneal adhesions and with difficulty reached by the exploring needle. So that the earlier literature of this subject is largely a record of mistaken diagnoses, the true condition, in many cases, having been discovered only after death or during operation for a supposed empyema or hepatic abscess. In this relation, Bristowe, after reporting two obscure cases, says: "It seems clear that the recognition of abscesses in the upper part of the abdomen is often extremely difficult if not

impossible, and that to diagnosticate them correctly demands the most careful and continued observation, and to treat them effectively calls for both skill and courage."

The gradual accumulation of observations, however, especially since the valuable article by Leyden, in 1880, on the condition which he termed "Pyo-pneumothorax Subphrenicus," [1] shows that latterly more cases have been recognized and attributed to their proper sources, and early treatment by incision and drainage has oftener led to recovery. But it is also apparent that the primary causative lesions are of so grave a character, and the complications so serious, that cure can result in no large proportion of cases.

CLASSIFICATION.

In a general way such abscesses may be classified according to their situation. They may be under the right or the left wing of the diaphragm, the suspensory ligament of the liver being the dividing limit. In the former case they are encapsulated between the diaphragm and the right lobe of the liver, and are usually due to inflammation extending from the region of the liver, kidney, duodenum, or cœcal appendix. On the left they find their seat in the tissues adjacent to the stomach, the pancreas, the left lobe of the liver, or the spleen, their lower limit being formed by firm adhesions between these organs, the transverse colon, and the parietes. This is the more common position owing to the fact that the most frequent exciting cause is perforating gastric ulcer. Subphrenic abscesses, so called, are usually within the peritoneal cavity, a circumscribed peritonitis, but they may be retro-peritoneal, extending in the connective tissue behind the stomach, duodenum, intestine, or kidney. They may contain air through perforative communication with the gastro-enteric tract, or they may not. Finally, they may invade the abdominal or the thoracic cavity, more frequently the latter, thereby giving rise to the most complicated physical signs and conditions.

THE ETIOLOGY

of these abscesses and the incidents attending their course may, perhaps, be best shown by the report of seven cases, which have come under my observation at the Boston City Hospital during the past

[1] Zeitschrift für klinische Medicin, 1880, S. 320.

five years, with such amplifications as the literature of the subject affords. I will then consider the difficulties attending their diagnosis and treatment.

CASES.

CASE I. (Mason.) *Abscess between liver and diaphragm; drainage; recovery.* —An Italian, aged thirty-five years, entered my service at the Boston City

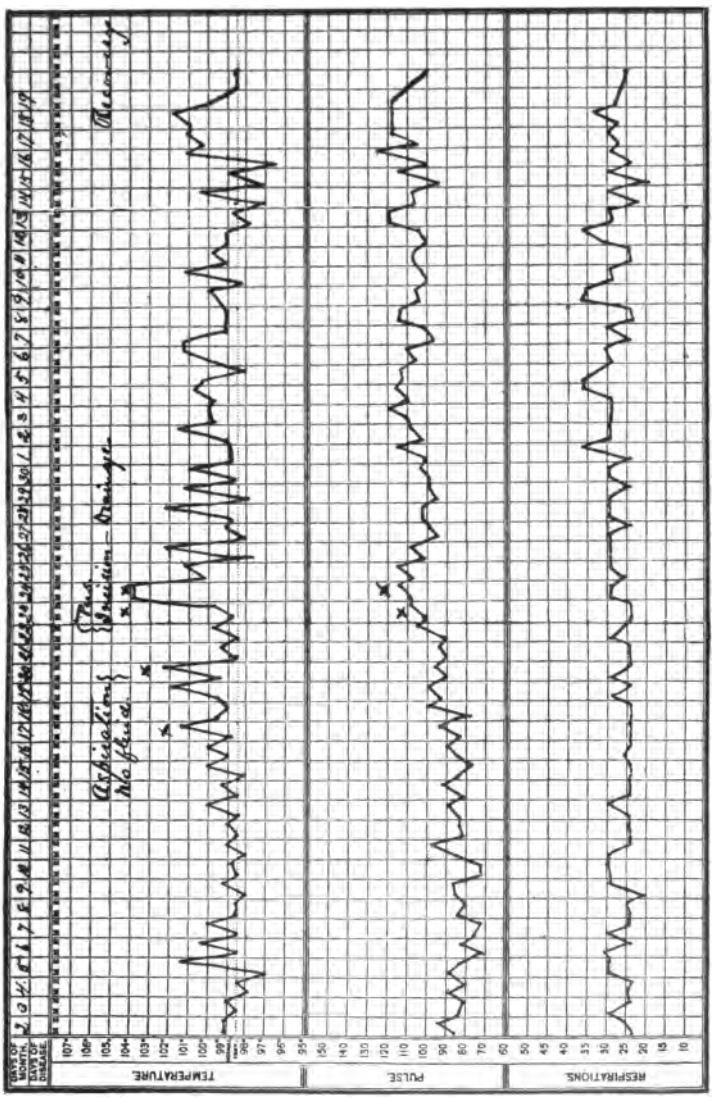


FIG. 1. Case I.

Hospital, with diarrhœa and iliac tenderness. He had little fever and no history of prolonged illness. The symptoms abated in a week, but ten days later abdominal pains, headache, and diarrhœa recurred. The spleen was not enlarged. Distinct diazo reaction in urine. Typhoid fever, dysentery, and malaria were considered and excluded. Pain at epigastrium and over liver increased, with distended stomach and vomiting, and soon the hepatic dulness was found to extend an inch and a half below the ribs in the mammary line. No jaundice. Respiration deficient at the right base. An examination of the blood showed 4,690,000 red corpuscles to 20,000 white (235 : 1)—a leucocytosis. Abscess in the region of the liver was suspected, but the exploring trocar at the angle of the scapula and in the side found no pus. A week later twenty-four ounces of inodorous pus were evacuated through the sixth space, anterior axillary line. Dr. F. B. Mallory, assistant pathologist to the hospital, examined the pus but found only broken-down material; pus corpuscles and large fatty cells; no organisms; nothing diagnostic. Dr. Edward H. Bradford, my surgical colleague, evacuated and drained the abscess through the seventh space at the anterior axillary line. Half a pint of pus escaped. The incision went through the diaphragm which was adherent to the costal parietes. The finger could feel the upper surface of the liver, but no cavity in its substance. Irrigation with boric acid solution; baked-gauze dressing. There was a yellow or pinkish discharge containing débris, which might have been liver substance, but this was not determined. Recovery in one month.

Similar cases are the following, which I find after brief search, and they are probably not very uncommon.

Case.—Stockton and Park[1] report a case of subphrenic abscess above the right side of the liver, thought to have been due to hepatic abscess, which was cured by operation. Two years later the patient had pleuritis, septic pneumonitis, and empyema, which were also cured by incision and drainage.

Case.—Ford[2] reports an interesting case of "Hepatic Abscess with Signs of Pneumothorax," obscure respiration, metallic tinkling, and succussion. The autopsy showed complete adhesion of the right lung to the parietes and to the diaphragm. The lower lobe was the seat of an abscess which communicated, through the diaphragm, with a large abscess of the liver, thus forming an air-containing cavity which had given rise to the signs of pneumothorax. The abscess had been treated by intercostal incision and drainage.

Case.—Fyffe,[3] in an article on "Abscess of the Liver," relates the following deceptive history: A patient from India who had had dysentery presented "liver symptoms," with bulging and fluctuation of the right side. Incision between eighth and ninth spaces in front and drainage of a supposed hepatic abscess. At the post-mortem, some time later, the liver was found to be perfectly healthy, but an abscess above it had made several spontaneous openings.

From this and other cases the author concluded that peri-hepatic abscess in this locality may find its way out by several openings; whereas, if abscess of the liver points externally, it is generally in

[1] International Medical Magazine, May, 1892.
[2] St. Louis Clinical Record, July, 1876.
[3] Bristol Medico-Chirurgical Journal, 1884, vol. ii. p. 250.

one direction by a single orifice, and that most frequently at the margin of the right lower ribs.

Case.—Cochrane[1] records a case of subphrenic abscess between the right lobe of the liver and the diaphragm, in which the symptoms and history had indicated hepatic abscess. Rupture into the right lung occurred and pus found exit through the bronchi. At the autopsy the liver was normal, but on its upper surface was an abscess bounded above by the diaphragm and below by the hepatic capsule, with an opening an inch in diameter into the base of the right lung.

Case.—Suppurating echinococcus cyst was the cause of subphrenic abscess in a case reported by Herrlich,[2] who resected the seventh rib in the right side, incised the diaphragm, and cured the patient.

Case.—Shepherd[3] relates the case of a man, aged sixty, at the Montreal General Hospital, who was thought to have liver abscess or echinococcus cyst. He had a history of pain at the epigastrium and right hypochondrium for more than a year, with slight jaundice. A fluctuating tumor pointed at the right hypochondrium and encroached upon the thorax, causing bulging. Eighty ounces of pus were evacuated. The diaphragm was felt through the opening pushed up to the third rib in front. The liver was displaced downward and backward, but was not felt. No signs of echinococci or liver substance. Rapid recovery. The abscess was peri-hepatic.

Case.—A. T. Cabot[4] reports from the Massachusetts General Hospital, "two cases of abscess of the liver, implicating the pleural cavity," which he cured. In the first, an incision through the tenth space, posterior axillary line, showed a large abscess below the diaphragm which had invaded the pleural cavity. In the second case, a higher incision in the seventh space anterior axillary line gave exit to a few ounces of pus from a sacculated empyema. The diaphragm was felt bulging up, was incised, and a large abscess below was drained.

It is evident from these cases that subphrenic abscess of the right side may arise by extension from hepatic abscess or echinococcus cyst, and also that it may not involve the liver substance at all. The distinction during life is very difficult. Dabney,[5] in his paper on "Hepatic Abscess," read before this Association last year, states that rupture into a bronchus is the most common and least dangerous direction. He also says that the presence of liver cells in the contents of an hepatic abscess does not seem to be of very common occurrence, but that occasionally they are found and are of great value in diagnosis. Von Jaksch[6] says that it rarely happens that much aid accrues to diagnosis from the chemical examination of purulent discharges. In Cabot's cases the microscopical and chemical examinations were thought diagnostic of liver abscess. In my case

[1] Canadian Practitioner, April, 1884.
[2] Deutsche med. Wochenschrift, 1886, S. 139.
[3] A Case of Sub-diaphragmatic Abscess. Phila. Med. News, December 17, 1887.
[4] Boston Medical and Surgical Journal, January 9, 1890.
[5] Transactions of the Association of American Physicians, 1892, vol. vii.
[6] Clinical Diagnosis, p. 298.

the result of microscopic examination was negative. In cases of "peri-gastric" abscess, to be mentioned later, streptococci and the bacillus pyocyaneus have been found, with many other organisms and sometimes particles of food. From this source, also, round worms have escaped into the pleural cavity.

SUBPHRENIC ABSCESS IN RELATION TO PERFORATING ULCERS OF THE STOMACH AND DUODENUM.

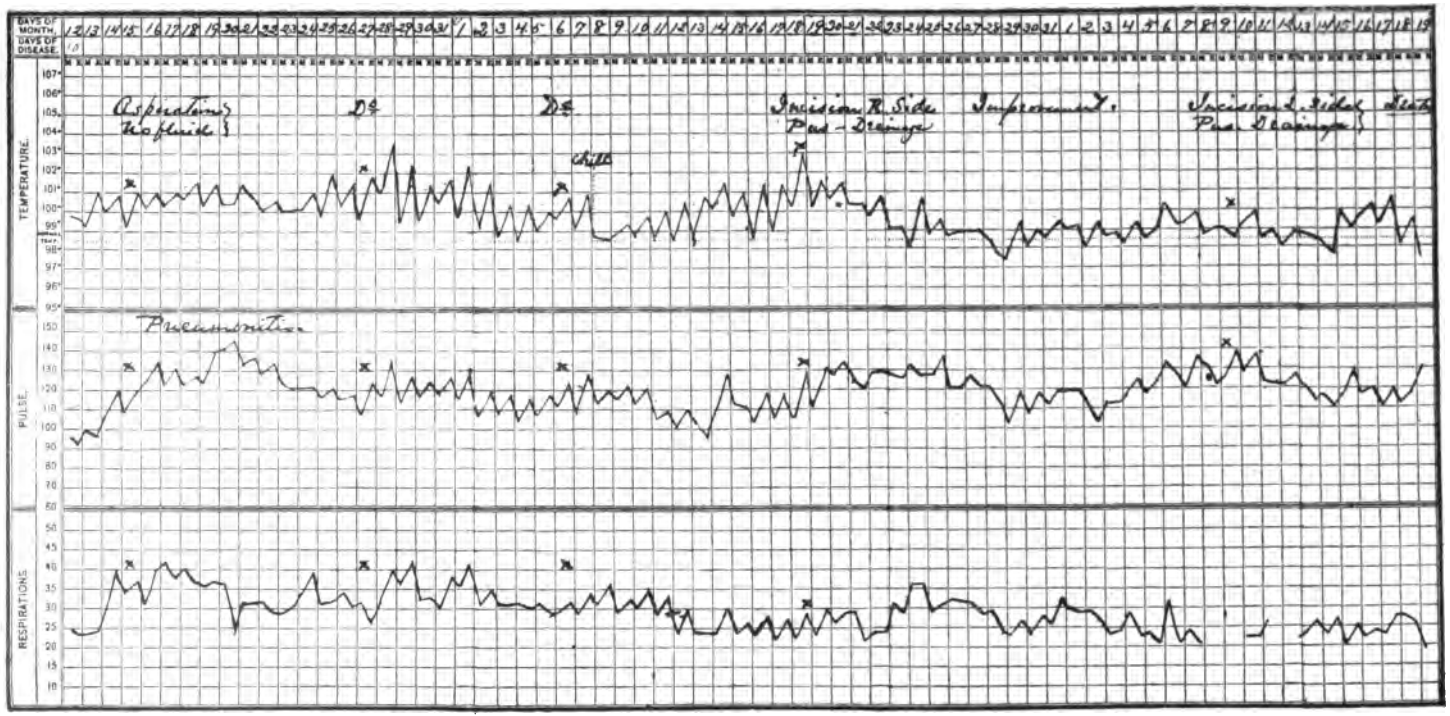
The chief interest of this subject, however, centres upon its relation to gastric and duodenal ulcers, and upon the occurrence of air-containing abscesses which present signs resembling those of pyopneumothorax. Four such cases have come under my observation. Two of these were reported to the Suffolk District Medical Society[1] four years ago, and will be briefly recapitulated. (Cases II. and V.)

CASE II. (Mason.) *Subphrenic abscess from gastric ulcer, with perforation; drainage; cicatrization of ulcer; death.*—A young woman, aged twenty-two years, who had been anæmic for a year, entered the hospital December 12, 1888, with dyspepsia and gastric pain. The pain was referred to the lower margin of the ribs, and was aggravated by forced inspiration. There was fever, but vomiting, chills, and sweating were absent. She had retention of urine. In the left side and back respiration was absent below the seventh rib; tubular above, with high-pitched, crackling râles. There was no cough. Aspiration in the seventh space found no fluid. Vomiting soon became a prominent symptom, the vomitus containing pus and blood-stained shreds, with a very foul odor, as if an abscess were discharging through the stomach. These evacuations were followed by relief of pain and diminution of fever. Further explorations failed to reach the pus. Shortly, the pain was transferred to the right side in the region of the lower ribs, with tenderness over the liver, which was neither enlarged nor depressed. There was severe pain in the right shoulder. I evacuated several ounces of pus, having the same odor as the vomitus, by incision through the tenth right space, anterior axillary line, and inserted a drainage-tube, which followed the surface of the liver four inches upward and backward. The cavity was washed out with creolin solution, and closed up in ten days. In the meantime, the pain, fever, and vomiting had abated, but the consolidation in the left back persisted. In a few days gastric pain and vomiting returned, but the vomitus had lost its offensive odor. Pus was now found at the seventh left space, axillary line, and the cavity was drained, but the patient soon died from exhaustion. Cough and expectoration had been absent throughout.

Autopsy: Both pleuræ adherent to chest walls. No fluid in pleural cavities. Lower lobe of left lung solidified and firmly adherent to diaphragm. On section, it presented a granular surface, and was very dense (interstitial pneu-

[1] See Boston Medical and Surgical Journal, October 31, 1889.

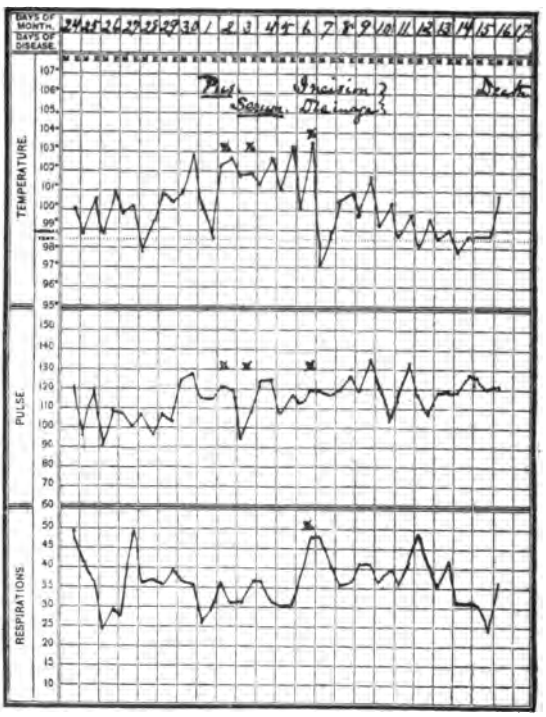
FIG. 12.



Case II.

monitis). In a space between the liver, spleen, stomach, diaphragm, and chest-wall was an abscess cavity, of three or four ounces capacity, which communicated with the incision in the left side. There was no perforation of the stomach, but in the posterior wall was a recently healed ulcer. Firm adhesions bound the above-mentioned organs together and to the parietes. The diaphragm was not perforated. The abscess in the right side had closed and the sinus could not be found. Liver, kidneys, and heart pale and opaque.

FIG. 3.

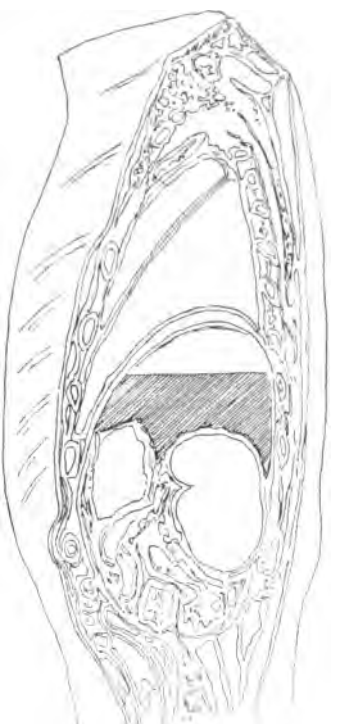


Case III.

CASE III. (Forster.) *Subphrenic abscess from perforating ulcer of the stomach; drainage; death.*—A female, aged thirty-five years, entered the hospital September 24, 1890, in the service of Dr. E. J. Forster, who asked me to see her. She had had dyspnœa and palpitation for a year; abdominal pain and vomiting for a week only. No hæmatemesis. Marked tenderness in the epigastrium, left hypochondrium, and lower part of left chest. Liver one inch lower than normal. In the splenic region flatness extended from the seventh rib to a point midway between the border of the ribs and the umbilicus. Here a tumor was felt which was stationary during deep respiration. Non-tympanitic fulness at epigastrium.

Lungs: Below angle of left scapula, flatness; diminished respiration, voice sounds, and fremitus. Succussion splash. No cough. Aspiration at seventh left space, posterior axillary line, found thin, foul pus. The following day, at nearly the same level, twenty-four ounces of clear serum were withdrawn. This seemed to show a serous pleurisy and an abscess cavity below.

FIG. 4.



Case III. (Diagram.)—Vertical section through stomach and spleen, to show relations of air-containing abscess.

A diagnosis of subphrenic abscess from perforating gastric ulcer was made, and operation was advised. This was undertaken by Dr. H. L. Burrell, Dr. D. W. Cheever in consultation, although in the meantime the patient had begun to expectorate a dark, foul, purulent fluid, and was so weak that ether was not administered. About two quarts of sanious pus escaped through a free incision in the ninth space, posterior axillary line. Irrigation with warm boracic acid solution. After four days the fluid came away clear, the cavity had contracted, and the temperature was normal, but there was no gain in the patient's strength, and she died ten days after the operation.

Autopsy: Below the ensiform cartilage a cavity was opened, of large size

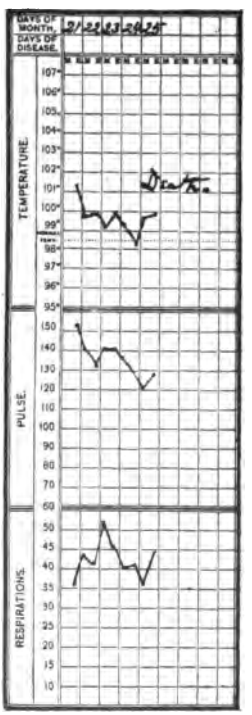
and lined with pyogenic membrane, bounded by the liver, diaphragm, stomach, and adhesions. The left lung was adherent to the chest-wall behind and to the diaphragm, leaving a pus cavity in the lowest part of the pleural sac from which was an opening through the diaphragm into the abscess below. Lower part of lung gangrenous; liver, stomach, and spleen firmly adherent and removed together. Upper third of spleen softened and covered with pyogenic membrane.

The stomach showed two ulcers near the pylorus, in the lesser curvature, one through the mucous membrane only; the other, one centimetre in diameter, with smooth, rounded edges, communicating directly with the abscess cavity.

Diagnosis: Ulcer of stomach, with perforation and abscess formation above and below diaphragm.

CASE IV. (Sumner.) *Perforating gastric ulcer, with circumscribed peritonitis, which later became general; death.*—A Swedish young woman, aged

FIG. 5.



Case IV.

nineteen years, entered the hospital in the service of Dr. A. M. Sumner, February 21, 1893. For a week she had had gastric pain and nausea. No

vomiting or chills. The day before admission she fell to the floor, writhing in agony. The pain was referred to the chest, later to the abdomen. She was in collapse on admission, and failed steadily. The abdomen was tense, tender, and tympanitic. She vomited once or twice. It was noted that there was dulness at the bases of both lungs, and a friction rub in the right axillary region. On the left, tympany below the fourth rib in front and absence of respiratory sound. She died in a few days. A general peritonitis was recognized, but the patient's condition was such as to forbid extended examination.

Autopsy: An abstract of part of the autopsy, which was made by Dr. Councilman, is as follows:

The peritoneal cavity contained 1200 cubic centimetres of thin, fetid pus. There was a circumscribed cavity containing pus, shut off from the general cavity, and bounded by the suspensory ligament of the liver, the diaphragm, the upper surface of the left side of the liver, the stomach, and the parietes.

Stomach: The stomach was adherent to the liver. In its anterior wall, just beneath the attachment of the stomach to the liver, and about the middle of the stomach, was a round perforation with smooth edges, one centimetre in diameter. On opening the stomach, there was a round ulcer of the mucous membrane, two and a half centimetres in diameter, corresponding to the external perforation. It was directly in the middle of the stomach. On the posterior wall, at a point exactly corresponding to the ulcer in the anterior wall, was a small ulcer through the mucous membrane only.

Lungs: Congested at bases; no adhesions. Apices indurated (fibrous), with numerous small caseous and calcareous masses and fibrous nodules.

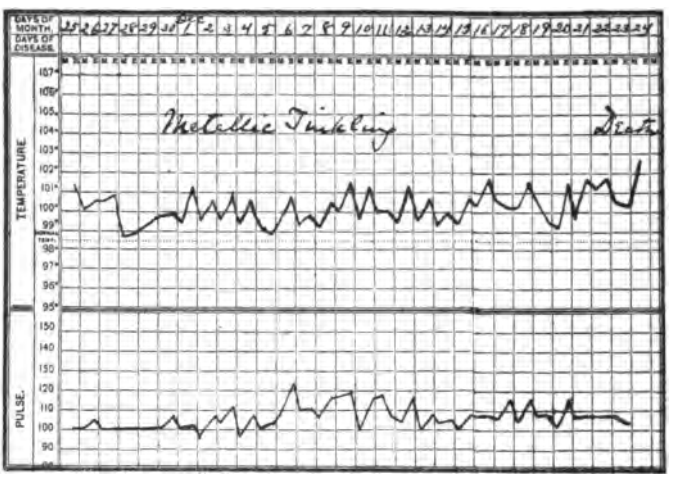
Pleuræ: Diaphragmatic pleura on both sides covered with fibrino-purulent exudation, which extended somewhat over the lateral surface of the left lung. 200 cubic centimetres of turbid serum in each pleural cavity.

Diagnosis: Perforating gastric ulcer causing circumscribed peritonitis with subsequent perforation of general abdominal cavity. Acute pleurisy with exudation due to extension from peritoneum. Old healed tuberculosis at apices.

CASE V. (Mason.) *Perforating duodenal ulcer causing abscess, with signs resembling those of pneumothorax; death; autopsy.*—Male, aged fifty-six years, entered the hospital November 25, 1888. After a severe gastric attack fifteen months before, he had recovered so far that he could work, but had never felt well since. A month before admission he was again seized with violent pain in the epigastrium and right side, so severe that ether was required. He had been in constant pain since, with several exacerbations. No vomiting and no blood from bowels at any time. At the epigastrium was a tense bulging, tender and resonant. Over this area metallic tinkling was heard when the patient coughed. The liver was two inches lower than normal. Over the front of the right chest, as low as the seventh rib in the mammary line, the percussion tone was hyper-resonant, the respiration was faint, vocal fremitus diminished, and metallic tinkling was heard. At times the coin sound was elicited, but these phenomena were inconstant, were not observed in the back, and there

was no succussion splash. In the lower half of the right back were signs of pleuritic effusion. The heart was displaced an inch and a half to the left. The removal of twenty-four ounces of clear serum by tapping at the fifth right space, posterior axillary line, gave relief to the pain and dyspnœa, and the epigastric bulging and tenderness disappeared temporarily, as well as the metallic tinkling. I had expected to find pus, thinking that a circumscribed pyopneumothorax was present, and I was at a loss to explain the signs, as this was the first of these cases which had come under my observation. Later tapping withdrew more serum, but no pus, the presence of which had been

FIG. 6.

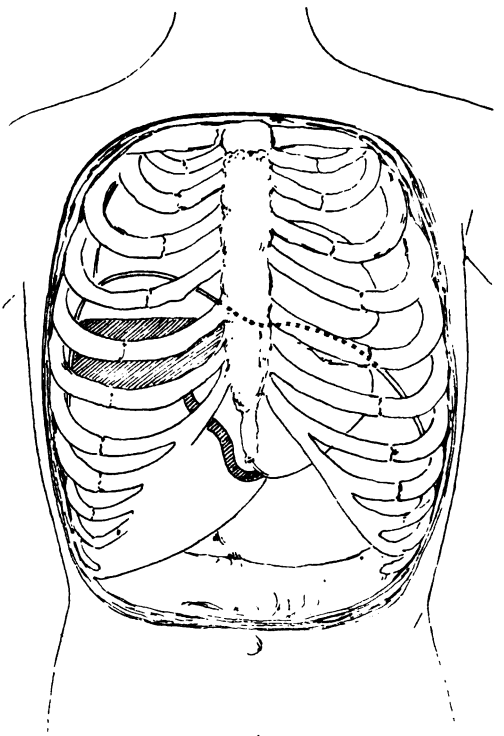


Case V.

suspected by Dr. Samuel Delano, who attended the case in its early stages, when the symptoms pointed rather to some abdominal affection. The patient failed gradually, and died in one month. There were no chills at any time. Cough and vomiting were slight. No pus was found in the stools.

Autopsy: Right lung adherent to diaphragm. Serous effusion in posterior right pleural cavity. Diaphragm not perforated. No pneumothorax. Lungs healthy. Between the right lobe of the liver at its highest part and the diaphragm was a large, circumscribed abscess, partly filled with pus, which communicated by a long sinus with an open duodenal ulcer one and a half centimetres from the pylorus. This ulcer was circular, one and a half centimetres in diameter, with smooth edges, and from it extended a fistulous tract running on the under surface of the liver, between the gall-bladder and the longitudinal fissure, to the anterior border of the liver, then up the superior surface until it entered the abscess cavity. The gall-bladder, duodenum, and liver were adherent, thus shutting off the abscess from the peritoneal cavity.

FIG. 7.



Case V. (Diagram).—Air-containing abscess above liver. Sinus communicating with duodenal ulcer.

REMARKS.

These four cases present in typical form the incidents which attend the course of subphrenic abscess when due to perforating ulcer of the stomach or duodenum. Two had a clear history of symptoms below the diaphragm and in two this history was wanting, but the secondary nature of the thoracic complications was suggested in all. In Cases III., IV., and V. the physical signs which accompany pyo-pneumothorax were present in a greater or less degree. Case V. was to me very obscure. The fluid in the pleura, the displacement of the heart, and the metallic sounds were very misleading. The abscess under the arch of the diaphragm, covered above by the adherent lung and behind by a large pleuritic effusion, was out of reach by the ordinary

means. It was observed, however, that the respiration and the vocal fremitus were not totally suppressed in front as they would have been in general pneumothorax, but it was only at the autopsy that the air-containing abscess above the liver was recognized as the cause of these peculiar phenomena.

In very few instances does the abscess caused by gastric perforation extend to the right side as in Case II. It is almost always limited by the falciform ligament, but occasionally an abscess due to gastric ulcer which perforates near the pylorus may seek its way to the convexity of the right lobe of the liver. I find but one case with perforation of the cardiac end of the stomach and one through the posterior wall in which this course was taken; and but one in which perforating ulcer of the duodenum caused abscess of the *left* side.[1] Eisenlohr[2] mentions the case of a girl in whom, at autopsy, was found a perforating gastric ulcer of the posterior wall, communicating with an abscess above the right lobe of the liver, which during life had given rise to tympany and metallic tinkling below the right scapula.

Therefore, an air-containing abscess under the left ala of the diaphragm almost invariably indicates perforating ulcer of the stomach, usually of the middle portion, in the lesser curvature, and most frequently in the posterior wall; whereas a similar abscess between the right lobe of the liver and the diaphragm points to perforation of the duodenum or vermiform appendix. I find but two instances in which abscess under the left wing of the diaphragm was traced to an appendicitis.[2]

Empyema and true pneumothorax are not infrequent results of perforation of the diaphragm from below, but the adhesion of the lung to the diaphragm and costal pleura tends to check this complication. The abscess may also be evacuated through the bowels or the bronchi, as in Case III. Serous or sero-purulent pleural effusion, from contiguity with the subphrenic abscess, is more common.

Fenwick,[3] in his interesting clinical lectures at the London Hospital on "Some Obscure Diseases of the Abdomen," mentions eight cases of peri-gastric abscess and five cases of "peri-duodenal" abscess

[1] Mittheilung. med. Klinik zu Königsberg, 1888, S. 211.

[2] Berliner klin. Wochenschrift, 1877, S. 539; and November 14, 1892.

[3] Clinical Lectures on Some Obscure Diseases of the Abdomen, by Samuel Fenwick, M.D. London, 1889.

as having occurred at that hospital during the past forty years. He also collected reports of fifty-one peri-gastric abscesses from various sources. Forty-one were caused by gastric ulcer, six by cancer, and four by lesions not connected with the stomach. While gastric ulcer is more common at the pyloric end, the greater fixity of the cardiac extremity is thought by this writer to favor the adhesions which admit of the formation of abscesses, as it is found that these usually communicate with ulcers in the lesser curvature nearer the cardiac orifice. In twelve cases the thorax was invaded, but in others there was empyema without perforation of the diaphragm. In twelve cases the abscess found exit through the parietes, and in three the pericardium was perforated, causing death on the third or fourth day. Pneumo-pericardium may supervene. Two-thirds of the patients were females, and the symptoms were often of many years' duration. Fever and pain were prominent symptoms, but repeated chills were not noticeable. Both true and false pneumothorax were often recorded. Pus from the abscesses in some instances contained food. In five cases the perforation of the stomach was found to have healed as in Case II.

At that hospital there were also five cases of "peri-duodenal" abscess during the same long period. Of twenty-four cases which Fenwick had collected, eighteen were caused by perforating ulcer of the duodenum, three by gastric ulcer, five by suppuration from gall-stones which burst into the duodenum, and one by hydatids of the liver. The ulcers were usually near the pylorus; they were seldom in an acute stage. The edges were smooth and thickened. In two cases the pus had made a cavity in the pancreas, and in five suppuration had extended to the connective tissue behind the duodenum. Peri-duodenal abscesses were more common in males. Nine out of eleven cases in which the sex was mentioned were in men. In one case the symptoms had existed for eight years, in another seven, in a third three, the ulcers having become quiescent, thus forming adhesions. Pain, radiating from the epigastrium, was the most notable previous symptom, but this was not always urgent. In most cases there had been vomiting of blood or bloody discharge from the bowels. Emaciation and exhaustion were often extreme. Tumor at the epigastrium was the most frequent sign on inspection, usually elastic, often tympanitic, and sometimes giving a metallic tinkling. The line of tympany in certain cases varied with the position.

I have been able to find no instance of recovery from this condition and know of no case in which a perforation of the duodenum has been found healed after death.

SUBPHRENIC ABSCESS FROM PERFORATION OF THE VERMIFORM APPENDIX.

That perforation of the vermiform appendix may give rise to abscess which extends to the arch of the diaphragm was observed by Duchek,[1] Bamberger,[2] Bernheim,[3] and other more recent writers, who have called attention to the interesting auscultatory features which air-containing abscesses in this region may present. Cossy[4] applies the term "false pneumothorax" (faux pneumothorax) to these misleading signs, and relates two cases of perforated appendix which presented this condition. In one case, on section, the anterior surface of the pericardium, when percussed, resounded like a drum, suggesting pneumo-pericardium, but this sound was found to be transmitted from the air-containing abscess beneath.

Similar cases of subphrenic abscesses of the right side with amphoric signs in the thorax are recorded by Jaffé[5] (Hamburg) and Herrlich,[6] who both operated unsuccessfully by thoracotomy. Large air-containing abscesses were found between the diaphragm and the right lobe of the liver and there was fistulous communication with the perforated appendix.

Starke[7] records a case of the same kind in which spontaneous cure followed the evacuation of the abscess through the bronchi.

Pätsch[8] effected a cure in the case of a boy, eighteen years old, who was seized four days before admission to the hospital with signs of peritonitis in the right iliac region. Two weeks later pain developed about the sixth and seventh ribs and there were signs of fluid encroaching upon the thoracic cavity without cough or expectoration. Exploration discovered foul pus, which soon after found exit through

[1] Präger Vierteljahrsschrift, 1853.
[2] Verhandl. der phys.-med. Gesellschaft zu Würzburg, 1858, S. 123.
[3] Virchow-Hirsch Jahresbericht, 1874.
[4] *Sur le Pneumothorax engendré par des Gaz provenant du Tube digestif.* Archives gén. de Med., 1879, ii. 526.
[5] Deutsche med. Wochenschrift, April 16 and 23, 1881.
[6] Ibid., 1886, xii., S. 139.
[7] Charité Annalen, 1882, S. 629.
[8] Ibid., S. 300.

the bronchi. Incision above the seventh rib in the anterior axillary line resulted in early recovery.

Taylor[1] relates a case in which a large abscess was found between the liver and diaphragm caused by extension from a sloughing appendix.

Fitz,[2] in his paper on "Perforating Inflammation of the Vermiform Appendix," read at the first meeting of this Association, says: "The extension of a secondary paratyphlitis may cause perforation of the diaphragm with a consecutive pleurisy or pericarditis." Such a case was then mentioned by Dr. W. W. Johnston, with the remark that such an untoward event would be rare at the present time, owing to early operative interference.

Leyden,[3] however, has lately recorded a case of "pyo-pneumothorax subphrenicus" in which an abscess containing more than two litres of pus had formed above the right lobe of the liver, having extended to this region through retro-cœcal suppuration, the result of perforative appendicitis. Intercostal drainage failed to cure, and after death it was found that the abscess had gone through the left wing of the diaphragm also. The hole in the appendix had closed.

PERI-SPLENIC ABSCESS.

Suppuration in the splenic region, except as the result of traumatism or pyæmia, is rare. But Zuber,[4] in an article on peri-splenic suppuration, reports cases of abscess in this region, the result of circumscribed peritonitis. They were bounded by the spleen, stomach, colon, and diaphragm, and were said to have been caused by an "infectious splenitis" attributed to the poison of intermittent fever. Cases by Hilton Fagge, Grisolles, Villemin, and others are quoted.

Wardell[5] refers also to the influence of malaria in causing latent splenic inflammation which may result in abscess below the diaphragm and secondary pleurisy or empyema. The same accidents may hap-

[1] Guy's Hospital Reports, vol. xix.

[2] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, vol. i., 1886.

[3] Berliner klinische Wochenschrift, Nov. 14, 1892.

[4] C. Zuber: Des collections purulentes péri-spléniques. Revue de Médecine, Paris, 1882, vol. ii. p. 928

[5] Contributions to Pathology and the Practice of Medicine. By John Richard Wardell, M.D., Edin., p. 72.

pen which result from abscesses in this region from other causes. The lung, stomach, or colon may be perforated.

Jaffé[1] tapped a subphrenic abscess at the angle of the scapula and removed bloody, offensive pus. After death the spleen was found to have been ruptured by an injury.

Herrlich[2] reports a case in which the diaphragm was pushed up to the third rib by a large metastatic abscess in the splenic region. The signs of pleuritic effusion were present and pus was obtained by aspiration. The patient died before thoracotomy could be performed, and the pleura was found to be free.

Councilman[3] reports the post-mortem examination of a case of perisplenic abscess with perforation into the splenic flexure of the colon, followed by thrombosis of the splenic vein and multiple abscesses of the liver, probably the result of an injury.

SUBPHRENIC ABSCESS FROM PERI-NEPHRITIC INFLAMMATIONS.

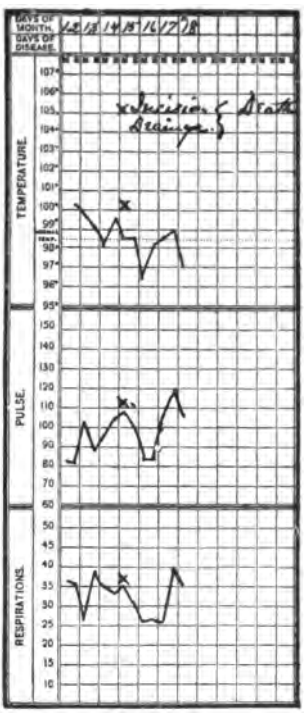
While lumbar tumor usually characterizes peri-nephritic abscesses, they may develop around the upper part of the kidney, and are then contiguous to the diaphragm. By extension they may penetrate the lung or pleura. It was in this class of cases that the late Dr. Henry Ingersoll Bowditch, in a timely article on "Peri-nephritic Abscess,"[4] urged the danger of chest complications and the importance of early and radical operation. He reported several cases which had come under his care. Roberts,[5] in a paper on "Peri-nephritic Abscess," also calls attention to the importance of chest symptoms in such cases. But they form a class by themselves, as a rule, with special symptoms, and I will not allude to them further except by the report of a case which illustrates the above-mentioned dangers.

CASE VI. (Mason.) *Peri-nephritic abscess involving the diaphragm and pleura.*—A man, aged thirty-three years, entered the hospital with the history of pain in the right hypochondrium for a year, but he had worked until the last week. He was emaciated and cachectic and had bulbous fingers. There were signs of fluid below the right scapula and tenderness over the lower

[1] Ueber subphrenische Abscesse. Deutsche med. Wochenschrift, April 16 and 23, 1881.
[2] Deutsche med. Wochenschrift, 1886, S. 139.
[3] Johns Hopkins Hospital Bulletin, No. 10, January, 1891.
[4] Medical and Surgical Reports of the Boston City Hospital, vol. i., 1870.
[5] Peri-nephritic Abscess. American Journal of the Medical Sciences, April, 1883.

intercostal spaces in the axillary line, with retraction of the same spaces in front, as if the lung were adherent. Liver and spleen enlarged and easily felt below the ribs. Urine, albuminous; large and small hyaline and granular casts. Ten ounces of foul-smelling pus were withdrawn by aspiration at the eighth space, posterior axillary line. The proximity to the diaphragm, the adherent lung, and the pain, gave rise to the opinion that there was a

FIG. 8.



Case VI.

latent subphrenic abscess with secondary empyema. The enlarged liver and spleen and the urinary changes suggested amyloid degeneration. An incision was made in the ninth space behind, and the cavity was irrigated, but the patient soon died from septicæmic exhaustion. Cough, expectoration, and râles, chills, sweating, and vomiting had been noticeably absent. The temperature was subnormal.

Autopsy : At autopsy the right pleural surfaces were adherent throughout, except at the lowest posterior part, where there was an abscess cavity. Below the diaphragm and surrounding the upper part of the kidney was another

abscess, the diaphragm being necrotic. Amyloid spleen and kidneys. Tubercular deposits in lungs and liver.

FIG. 9.

Case VI. (Diagram).—Peri-nephritic abscess (tuberculous); secondary empyema—back view.

GALL-STONES.

Gall-stones show little tendency to excite suppurative processes in their vicinity. Fenwick cites five cases in which they had caused abscesses which burst into the duodenum, but such instances are rare and their course is more acute than that of the abscesses caused by perforating ulcers.

SUBPHRENIC ABSCESS FROM CANCER.

Cancer is an infrequent source of sub-diaphragmatic abscess, but such cases are referred to by Andral,[1] Habershon,[2] and Fenwick.[3] Neusser[4] relates the following: A woman, aged thirty-six, had a large

[1] Clinique Méd. d'Andral, t. ii. p. 64.
[2] On the Alimentary Canal.
[3] Loc. cit.
[4] Wiener med. Wochenschrift, 1884, No. 44.

cavity filled with pus and air between the liver and diaphragm on the right side, communicating with a deeply ulcerated cancer of the pylorus which had been diagnosticated during life. There was perforation of the diaphragm and gangrene of the lung.

LITERATURE.

When we turn to the literature of this subject we find that it is fragmentary, but it is no less interesting to watch the progress of auscultatory science and physical observation than the advance of surgical art in dealing with these difficult cases.

In 1829, Wright[1] records two cases of "pneumo-hepatic" abscess as occurring at the Baltimore Almshouse. In one there was recovery after the spontaneous discharge of air and pus between the eleventh and twelfth ribs near the spine. Pain, fulness and threatened suppuration at the epigastrium were noted, and were attributed to abscess of the left side of the liver, but the diagnosis was uncertain. In the other case there was a double abscess, containing air, in the lung and the liver, with communication through the diaphragm.

Graves and Stokes[2] record a similar case in which an abscess resting on the convex surface of the liver had involved the lower lobe of the right lung. Incision between the eighth and ninth ribs gave exit to a pint of sanious pus. Through the opening air escaped with force on coughing. The autopsy showed that the diaphragm had been perforated, but it was not clear whether the pulmonary abscess or the one below the diaphragm was primary.

The recognition of the relation between perforating gastric ulcer and the signs resembling pneumothorax has been attributed to Barlow and Wilks, who first reported such a case in 1845, under the title, "Perforation of the Stomach, with Obscure Thoracic Symptoms."[3]

Case.—A female, aged thirty-nine years, was admitted to Guy's Hospital, October 26, 1844. History of gastric ulcer for eighteen months. Two days before admission she had an attack of sudden dyspnœa and intense pain. The epigastrium was prominent, very resonant, and tender. There were signs of pleurisy at the left base, with also amphoric respiration, metallic tinkling, "Punch's voice," and succussion splash. Over the præcordia was a rubbing sound, synchronous with the heart-beats and heard when the patient held her breath. This was thought to denote pericarditis. Death took place twenty

[1] American Journal of the Medical Sciences, 1829, vol. iv. p. 353.
[2] Dublin Hospital Reports, 1830, vol. v.
[3] London Medical Gazette, 1845, vol. i., No. 5, p 13.

days after entrance. "The stethoscopic signs, particularly the amphoric respiration, coupled with the severe symptoms, satisfactorily proved to many that the case was one of pneumothorax. Dr. Barlow was opposed to this opinion and persisted in referring the amphoric and metallic sounds to the stomach, and mentioned a case in which a perforation of the stomach had communicated with a large peritoneal abscess." This proved to be the case, and, although there was a pleural effusion, no communication existed between the chest and the abscess below the diaphragm. There was no pericarditis.

Case.—Williams,[1] in 1845, recorded the case of a man, forty years old, who, after dysentery, had an abscess between the right lobe of the liver and the diaphragm, which was later incised at the right hypochondrium. After death it was found that the metallic tinkling which had been observed had been produced by a communication between the abscess and the transverse colon.

Wintrich[2] says that when he was clinical assistant at Würzburg a mistaken diagnosis was made in the case of a woman in whom there was a large abscess cavity filled with gas, débris of food, and pus, connected with a perforating ulcer of the stomach. Pneumothorax was diagnosticated from the presence of metallic tinkling and percussion note, amphoric breathing, dyspnœa, cough, and expectoration.

Habershon,[3] Bouchaud,[4] Hilton Fagge,[5] Taylor,[6] and others have recorded a variety of cases of this description. Fagge's sixteen cases of "Abscess of the Upper Abdomen" from various causes are especially interesting.

But the subject attracted little general attention until 1880, when Leyden[7] published his well-known article entitled "Pyo-pneumothorax Subphrenicus," a designation which is evidently open to objection, but which explains itself clinically. From Leyden's clinic, through Herrlich,[8] Pfuhl,[9] Scheurlen,[10] and other writers comes a large part of our information on this subject. Leyden's original article related to four cases of air-containing abscess below the diaphragm. After having, in the first case, diagnosticated pyo-pneumothorax in a twenty-three-year-old female, he found, to his surprise, post-mortem, that the signs were produced by an abscess above the liver, which communicated with a perforating ulcer of the duodenum. After this experience he correctly diagnosticated three similar cases,

[1] London Medical Gazette, December, 1845.
[2] Krankheiten der Pleura. Virchow's Handbuch, Bd. v., Abth. ii. p. 358.
[3] Loc. cit. and Guy's Hospital Reports, 1885, iii. 1.
[4] Bulletin de la Soc. Anat. de Paris, 1862.
[5] Guy's Hospital Reports, 3d series, xix. p. 320.
[6] Loc. cit.
[7] Zeitschrift für klin. Med., 1880, Bd ii. p. 320.
[8] Loc. cit.
[9] Berliner klin. Wochenschrift, 1887, No. 5.
[10] Charité Annalen, 1889, xiv.

one duodenal and two gastric perforations. All proved fatal in spite of surgical treatment, carried out in one case by Langenbeck. In another case six exploratory aspirations failed to find the abscess, which, after death, was seen to originate in the vicinity of a closed gastric ulcer, which the author regarded as its undoubted cause.

Leyden's diagnostic points were, in part:

1. Previous abdominal symptoms, and absence of signs of thoracic disease in the early part of the illness.

2. Little displacement of the heart or bulging of interspaces.

3. Normal respiration under the clavicle, with abrupt transition lower down to the metallic and amphoric sounds which occur in pneumothorax.

But it is to be observed that the heart is often displaced by the coincident pleural effusion, as in Case V., and abrupt change in percussion tone is not always found. Moreover, the lung often adheres to the diaphragm and parietes, with partial loss of contractility, so that, although there may be a diminution in the breath sounds and vocal fremitus, they are not entirely abolished as in general pneumothorax. Cough and bronchial discharge aid us in diagnosticating a circumscribed pyo-pneumothorax.

From Leyden's clinic and other sources, chiefly German, Scheurlen[1] collected 34 cases, including two of his own, in one of which a cure resulted after resection of the ninth left rib in the anterior axillary line. The cause was perforating gastric ulcer. Half the cases were diagnosticated during life and 15 were operated on. Six recovered, but in one only was the cause a perforating ulcer. The earliest cure was recorded by Pätsch in the case of subphrenic abscess from appendicitis quoted above. The seat of the abscess was on the right side in 19 cases; on the left in 15. The causes were gastric ulcer, 11; duodenal ulcer, 4; perforation of vermiform appendix, 6; trauma, 3; hepatic or peri-hepatic abscess, 2; peri-splenic inflammation, 2; cancer of pylorus, 1; suppurating echinococcus cyst, 1; a swallowed hairpin, 1; and in 3 the cause was not determined. Pleural effusion existed in 16 cases; in 6 there was perforation of the lung through the diaphragm; in 2 pyo-pneumothorax, and in several others the deceptive signs which simulate that condition.

[1] Charité Annalen, 1889.

Scheurlen regards the absence of the usual causes of empyema, viz., tuberculosis, pneumonia, and the puerperal state (to which might be added the acute fevers), as important in aiding a diagnosis by exclusion. As valuable physical signs, he mentions the friction sound of dry pleurisy near the diaphragm, and the disappearance of the semilunar space in the left side, which occurs in pleurisy with very large effusion only. But without exploratory puncture, Scheurlen thinks that subphrenic abscess can be suspected only, not diagnosticated. He states that the pus is always ichorous, which is questionable. The withdrawal of pleuritic serum from one interspace, and of pus from a lower level is a valuable indication, which was also observed in our Case III.

A more recent communication from Leyden and Renvers[1] reports the cure of a peri-gastric abscess by puncture drainage. A large trocar was passed through the seventh space and the diaphragm. Through the canula, by means of a Nélaton catheter, the cavity was washed out without involving the pleura. Recovery ensued in one month.

This is by no means an exhaustive review of the subject, but there are few individual records of more than one or two cases, and I will refer to some of the more interesting ones as briefly as possible. Bristowe[2] reported two cases in an article on "Abscesses in the Upper Part of the Abdomen;" and more recently Dickinson and Ewart,[3] of St. George's Hospital, have recorded "two cases of perforating ulcer of the stomach with misleading physical signs," one of which, entitled "Perforation, with Supposed Pneumothorax," is similar to others which have been quoted. But the second, "Perforation, with Supposed Pericarditis," deserves attention.

Case.—A chlorotic girl, aged twenty-four years, was admitted with symptoms which were considered those of perforating gastric ulcer. There was pleural friction in the left axilla, and over the præcordia were tenderness and friction sounds which had all the characteristics of those heard in pericarditis. Syncopal attacks. These signs appeared to indicate that in addition to peritonitis and pleurisy there was also pericarditis.

Autopsy: Perforation of the posterior wall of the stomach, with peritonitis, which was almost restricted to the left half of the diaphragm and the upper surface of the left lobe of the liver. The abscess pushed up the left side of the diaphragm, which showed pleurisy on its upper surface. Soft lymph coated the lower parts of the left pleural membrane. *No pericarditis.* The roughened pleural surfaces, diaphragmatic, costal, and pulmonary, had given rise to a friction rub synchronous with the heart's action.

[1] Berliner klin. Wochenschrift, Nov. 14, 1892.

[2] Lancet, September 29, 1883.

[3] Lancet, March 7, 1891.

This pleuro-pericardial rub was noted in the original case of Wilks and Barlow, and the mode of causation was then also observed. It also occurs in pneumonia, with pleurisy, of the left side, and Flint states that in character this sound cannot be distinguished from the true pericardial friction. But the graver symptoms of pericarditis are usually wanting.

Case.—An interesting case is that of Schenck.[1] A woman was operated on for subphrenic abscess by resection of the eighth rib. Pneumothorax was caused thereby, and the upper surface of the diaphragm was united to the parietes before incision of the abscess to keep the pus out of the pleural cavity. The patient died, however, of sepsis, and at the autopsy transposition of the viscera was found.

Flint, in his *Practice of Medicine*, refers to the observations of Leyden and gives his conclusions, but does not mention having met with similar cases in his own experience.

Gee[2] says: "An abscess below the diaphragm may become partly filled with air and may so raise the diaphragm as to give a tympanitic percussion note over the lower part of the chest, but not the amphoric signs of pneumothorax."

This is evidently an error, which was pointed out by Coupland in the *British Medical Journal*, March 23, 1889, where he reports a case of subphrenic abscess of the right side, with signs of pneumothorax, probably caused by perforation of the vermiform appendix, and cured by operation.

As the editor of the posthumous work of the late Dr. Wilson Fox,[3] on *Diseases of the Lungs and Pleura*, Coupland has appended a concise description of the condition now under consideration, reproducing Leyden's plate.

Strümpell[4] had repeatedly seen perforation into the left pleural cavity from gastric ulcer, with septic pleurisy and sometimes pulmonary gangrene. Therefore, he says: "Whenever we meet a case of apparently spontaneous left-sided empyema we should at any rate always think of the possibility of gastric ulcer."

In Pepper's *System of Medicine*,[5] in the article by Welch, on "Simple Ulcer of the Stomach," attention is called very clearly to

[1] St. Petersburger med. Wochenschrift, April 8, 1889.
[2] Auscultation and Percussion.
[3] A Treatise on Diseases of the Lungs and Pleura. By Wilson Fox, M.D.
[4] American edition, 1887, p. 361.
[5] Vol. ii. pp. 499, 500.

the etiology of the class of cases under discussion, and the conclusions of Barlow and Leyden are quoted. The author also mentions Pfuhl's experiment with the manometer in Leyden's clinic, which goes to show that the pressure in the abscess cavity rises during inspiration and falls during expiration, the reverse being true in the pleural sac. But it is stated that Schreiber[1] has shown that this point does not hold good when the diaphragm moves little, as is often the case in this affection.

Osler[2] says: "The condition of pyo-pneumothorax subphrenicus may simulate closely true pneumothorax."

Vierordt,[3] in speaking of "Subphrenic peritonitis," says: "We understand by this an ichoro-purulent, sacculated peritonitis below the diaphragm. From paralysis, partly also from irritation, the diaphragm is pushed very high into the thorax, causing a marked retraction or compression of the lung of that side. That half of the thorax is broadened, and by the presence of pus and gas in the cavity, one is apt to mistake the condition for pyo-pneumothorax. Peritonitis of this character usually begins at the stomach, as an ulcer, or at the intestine, especially at the vermiform appendix or cæcum. In making a differential diagnosis, we observe whether, in the *status præsens* or in the previous development, there were indications of disease of the lungs, or, on the other hand, of the abdomen; and also whether the lung of the diseased side still performs the motions of respiration."

DIAGNOSIS.

The diagnostic points in these varied conditions have perhaps been sufficiently indicated by the foregoing citations and cases, but it seems to me that enough stress has not been laid upon the incompleteness and inconstancy of the signs in "false pneumothorax" as compared with the true, or upon their peculiar localization both above and below the usual position of the diaphragm. The metallic sounds may be loudest at the epigastrium. The adhesion of the lung to the diaphragm and parietes is an important indication of the inflammation below, as is the dry pleurisy which precedes this adhesion. A serous or purulent effusion in the back is misleading, but the patients always

[1] Ueber Pleural and Peritoneal-druck. Deutsches Archiv f. klin. Med., July 31, 1883.
[2] Practice of Medicine.
[3] Medical Diagnosis, 2d edit., 1892, Stewart's translation.

appear to be in much worse condition than a simple pleurisy would cause. Diaphragmatic hernia may present similar physical signs, but the history, usually of traumatism, is different.

PROGNOSIS AND TREATMENT.

The prognosis depends almost entirely upon the efficacy of surgical treatment by free incision and drainage, although cases of spontaneous evacuation and cure are not unknown. Tillmanns,[1] of Leipzig, in his article relating to the operative treatment of abscesses resulting from communication between the gastro-enteric tract and the thorax, reports a successful case of thoracotomy in a boy, fifteen years old, in whom a supposed intestinal perforation had caused an abscess which found its way through the diaphragm. Feculent-smelling fluid, which contained food, was evacuated from the right pleural cavity and recovery ensued. Tillmanns, after an elaborate discussion of twenty-two cases, expresses the opinion that the cure of subphrenic abscess may be effected by antiseptic drainage when the suppuration is not too extensive, if it remains shut off from the peritoneal cavity, and if the intestineal or stomach perforation heals spontaneously.

That the gastric ulcer may heal spontaneously without external drainage of the abscess is shown by the fact that cicatrization was observed in Leyden's case mentioned above, and in the following, in which the pus escapd through the bronchi or into the pleural cavity.

Case.—Southey[2] reports a case of prolonged pain and vomiting, with tender tumor at epigastrium. Hæmatemesis and melæna. Later, cough and fetid expectoration. Cancer was suspected. Autopsy showed a lage abscess between the diaphragm and the left side of the liver, the stomach, and the spleen. Perforation of diaphragm into lung and pleura. A sinus from the abscess led directly to the cicatrix of a round ulcer in the posterior wall of the stomach. No perforation of stomach remained.

Case. (Rigal.[3])—Man, fifty years old. Sudden attack of epigastric pain, with swelling. Later, signs of pneumothorax. At autopsy, a large abscess between liver, stomach, and diaphragm, and on posterior wall of stomach, 4 cm. from pylorus, two recently cicatrized ulcers.

Other similar cases might be cited. Fenwick mentions five in which, after death, the perforation was found to have healed. In my case, No. II., the same result appeared to have followed the drainage of

[1] Ueber die Communicationen des Magen-Darmcanales mit der Brusthöhle und über subphrenische Kothabscesse. Archiv f. klin. Chirurgie, 1881, S. 103.

[2] Med. Press and Circular, November 5, 1879.

[3] Bulletin de la Soc. Méd. des Hôpitaux, 1874.

the cavity, as the offensive vomiting ceased and great general improvement ensued, but the abscess reappeared on the other side, and the patient died. At the autopsy the ulcer was found closed.

Perhaps, as has been suggested, distention of the stomach ceases after perforation, and this may promote cicatrization. In any event, such a possibility enables us to form a more favorable prognosis in those cases in which posterior intercostal drainage of the abscess is resorted to, or when laparotomy may be undertaken with a view to sewing up the perforation, but the ulcer proves to be inaccessible. This I think, from the evidence of the autopsies I have seen, would usually be the case, the adhesions are so extensive and so dense; and in all operations the danger of involving the general peritoneal cavity must be considered.

In many of the later reports subphrenic abscesses have been diagnosticated promptly, and the necessary surgical procedures have been resorted to. The record of 100 cases, of which 20 were from American sources, shows 20 recoveries. The first cure in Leyden's clinic was in 1882, and most of the successful cases are those in which the operation was for abscesses in the right side associated with the liver or vermiform appendix. As before stated, I find no case of subphrenic abscess caused by perforating ulcer of the duodenum, in which cure has resulted, or in which the perforation has been found cicatrized after death. In but seven cases, when the abscess was under the left ala of the diaphragm and caused by gastric ulcer, has recovery taken place, so far as I am aware. One was reported by Barton,[1] in which the abscess opened into the bowel with a discharge of foul pus, and two other cases of spontaneous recovery are mentioned by Leyden.

Case.—Debove and Rémond,[2] at the Hôpital Andral, report the following: A female, aged thirty-three, had had for three years intense gastralgia, hæmatemesis, and epigastric tympany, which extended over the left lobe of the liver. Tapping evacuated foul pus and air, and laparotomy revealed a large abscess behind the liver, with prolongation toward the spleen. Cure in two months.

The author stated that this was the first recorded cure of this condition. But Von Hösslin,[3] from Ziemssen's clinic, has reported a

[1] Med. Press and Circular, 1890, p. 453.

[2] Des Abces gazeux sous-diaphragmatiques par Perforation des Ulcères de l'Estomac. Gazette des Hôpitaux, 1890, p. 1150.

[3] Münchener med. Wochenschrift, January 18, 1887.

case in which, from the symptoms and the character of the pus, perforation of the stomach was thought to have existed:

Case.—Female, aged thirty years; cyanotic. Respiration, 60; pulse, 120. Left lower ribs motionless. Heart displaced to right. Resection of seventh rib, anterior axillary line, opened a subphrenic abscess communicating with the pleura through an aperture in the diaphragm. During the next day the patient was livid and collapsed, and seemed at the point of death. But she rallied and recovered in seven weeks. A drainage-tube was pushed up through the aperture in the diaphragm and thus the pleural cavity was irrigated.

Scheurlen's case of recovery after resection of a rib is mentioned above, also Renvers's by puncture-drainage, but these are the only other cases that I have found.

Evidently the chance of life is a poor one under any circumstances when perforating ulcer of the stomach or duodenum is at the bottom of the trouble; but when the abscesses are connected with the liver, the kidney, or the vermiform appendix, the outlook is more favorable. These are mostly on the right side, between the liver and the diaphragm, and of such cases recovery took place in thirteen instances, twice by spontaneous evacuation through the bronchi after appendicitis. Resection of a rib was resorted to in a few of these cases only; in the others a simple incision was made. As was stated above, liver abscess is sometimes cured in this manner, and should hardly be included in the present subject.

Usually pleural adhesions prevent the opening of the pleural cavity by the knife, but in some cases the diaphragm has been incised through the pleura with a resulting pyo-pneumothorax. In one such instance an epigastric incision was followed by two posterior openings for better drainage. Clear serum flowed, followed by pus. Pyo-pneumothorax ensued, pyæmic abscesses formed in the brain, and death resulted.

This shows the importance of a low incision. The place should be determined by previous careful explorations at more than one level. In those cases in which there is epigastric tumor, laparotomy and search for the ulcer should be resorted to, but posterior drainage also will usually be necessary. I can find no record of a successful procedure of this nature. Fitz[1] relates the case of a woman, aged forty-one years, who came to the Massachusetts General Hospital with severe epigastric pain and a history which pointed to a per-

[1] Boston Med. and Surg. Journal, 1890, p. 583.

forating gastric ulcer. He advised laparotomy, but it was persistently refused by the patient, who died. Autopsy showed an abscess below the diaphragm, shut off by adhesions and containing air. The stomach was adherent to the adjacent organs, and had a perforating ulcer on the anterior wall.

The question of "Laparotomy for Perforating Ulcer of the Stomach" is discussed by Weir,[1] who calls attention to the frequency with which this cause of fatal peritonitis is overlooked. In one case he operated, emptied a subphrenic abscess, and sewed up a round perforation half an inch in diameter in the middle of the anterior surface of the stomach near the lesser curvature. The patient died from collapse, having suffered from peritonitis for four days before she entered the hospital.

Most of the ulcers, however, are on the posterior wall and very inaccessible on account of the adhesions. Under these circumstances, Weir recommends making a good-sized hole in the gastro-colic omentum and trying to examine the posterior wall in this way, or making a direct cut of large size into the stomach itself. This procedure has once come under my observation in the case of a young woman who for three years had presented the symptoms of gastric ulcer. The pain was so great that she insisted on laparotomy, which had been suggested to her. Dr. Bradford incised the stomach and with the electric light examined the interior, but no ulcer could be found. If it had existed it had healed. But the operation was entirely curative of all the symptoms

Thus far the results of laparotomy for gastric hemorrhage have not been very encouraging, and it is improbable that those for perforating ulcer will be more so. But the chance should be taken.[2] In many instances the patients are so exhausted that a prolonged operation cannot be completed. Weir relates such a case and one came under my observation this year at the City Hospital, in which laparotomy was performed by Dr. Cheever.

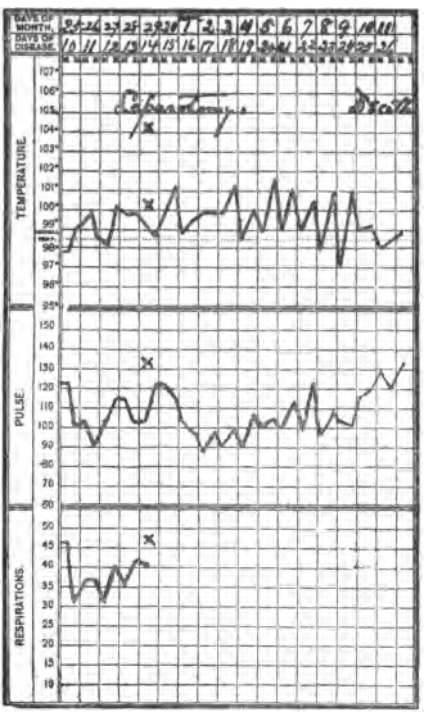
CASE VII. (Mason.) *Peri-gastric abscess; laparotomy.*—A Russian, aged twenty-two years, entered my service at the hospital with severe epigastric pain. In a few days there was a bulging, flattening on percussion, at the epi-

[1] International Medical Magazine, February, 1892

[2] See articles by W Nissen, St. Petersburger med. Wochenschr., 1890, lxiv., S. 516; and by Simon and Barling, British Medical Journal, January 9, 1892.

gastrium. The heart was displaced to the left. Subnormal temperature. No vomiting. The aspirating-needle withdrew, first a clear fluid of strawberry-juice color from the epigastric area, and then several ounces of offensive pus from a deeper level. Dr. D. W. Cheever performed laparotomy. The ex-

FIG. 10.



Case VII.

ploring finger discovered a large cavity, with trabeculæ, adjacent to the stomach, but the condition of the patient was such that further examination was not practicable. He rallied, however, and the abscess cavity was irrigated daily. A discharge of sloughy, purulent material continued, pain did not diminish, and he died from exhaustion in two weeks. There was no autopsy, and the cause of the abscess was undetermined.

CONCLUSIONS.

1. Subphrenic abscess, so called, is usually due to a circumscribed peritonitis, but may be retro-peritoneal.

2. The causes are: Perforating ulcer of the stomach, duodenum,

or vermiform appendix, rarely of some other part of the intestinal tract; hepatic, peri-hepatic, peri-splenic, and peri-nephritic inflammation; occasionally gall-stones, cancer, or echinococcus cyst. Sometimes the cause cannot be determined.

3. Air-containing abscess below the diaphragm, through communication with the gastro-enteric tract, may give rise to signs resembling those of pyo-pneumothorax.

4. Subphrenic abscess, when dependent upon perforation of the gastro-enteric tract, usually results fatally. But the prognosis is more favorable in those cases which follow perforative appendicitis than in those which result from gastric or duodenal perforation.

5. The perforating gastric ulcer, which is the cause of the subphrenic abscess, may heal spontaneously after the evacuation of the abscess, and early diagnosis would greatly reduce the hitherto reported large mortality.

6. Hepatic, peri-hepatic, or peri-nephritic abscess, which presents itself under the arch of the diaphragm, may often be successfully treated by intercostal incision and drainage.

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ON SUBPHRENIC ABSCESS.

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THE master of physical diagnosis, Wintrich[1] was about the first one to mistake an air-containing subphrenic abscess for pyo-pneumothorax. "I made the wrong diagnosis," he says, "because I put too much reliance upon the physical signs." By physical signs we can ascertain that there is liquid, with or without air, in a cavity lying within the thorax, but we can hardly rely upon them to decide whether the fluid is located above or below the diaphragm. Experience taught us that this movable partition can, by an accumulation of pus below it, be pushed high up in the thoracic cavity, thus simulating empyema or pyo-pneumothorax. To arrive at a correct diagnosis we are, then, bound to take many other points into consideration, and it seems to be the universally accepted view that it is chiefly the etiology which decides between empyema and subphrenic accumulation of pus. Leyden,[2] to whose classical study of the clinical features of the subphrenic abscess we owe our main knowledge on this subject, says, among other things, that if in a patient with symptoms of effusion in the thoracic cavity there has never been, during, or at least not in the beginning of the disease, any cough or other signs indicating trouble in the supra-phrenic cavity; and if, on the other hand, the present ailment was preceded by disturbances in the abdominal organs, we are justified in diagnosticating the effusion as a sub-phrenic abscess. This statement implies, of course, that the primary causes giving rise to the always secondary subphrenic abscess are exclusively located within the abdominal cavity. Leyden established his

[1] Wintrich: Virchow's Handbuch der speciellen Pathologie.

[2] Leyden: Ueber Pyo-pneumothorax Subphrenicus. Zeitschrift für klin. Medizin, Bd. i. S. 320.

diagnostic remarks on the basis of only ten cases. Since then the number of the reported cases of subphrenic abscess has increased at least tenfold. Some of the diagnostic points set up by Leyden have not been confirmed, but there seems to be a consensus of opinion as to the decisive value of the etiology in the diagnosis of subphrenic abscess.

It is not my purpose to deny this value, but it occurred to me that the unrestricted reliance upon the etiology, like the unconditional reliance upon the physical signs, must lead in one case or other to a wrong diagnosis. My objections to the unqualified reliance upon the etiology for differential diagnosis between empyema and subphrenic abscess are twofold. In the first place, there are a few cases of subphrenic abscess the primary cause of which is located in the cavity above the diaphragm. Secondly, there are cases of intrapleural effusion with an exclusive and pronounced abdominal history. My attention was drawn to these exceptions by the observation of a case of the kind mentioned first; lobar pneumonia was the precursor of a subphrenic abscess. Permit me to present to you a brief report of this case.

Alfred A., a perfectly healthy child of twenty-six months, became sick with high fever. The onset was abrupt. During the first five days there were present only general symptoms usually accompanying high fever. The fever had a continued character, 105° even in the morning, pulse 130, respirations 32, without characteristic features. No cough. On the sixth day physical signs indicating pneumonic infiltration appeared in a small area beneath the right clavicle. Dulness, tubular breathing, and bronchophony were present. On the ninth day the same physical signs appeared also in the back, in the right fossa supraspinata. Neither in the back nor in front did the signs of consolidation spread downward. The pneumonic fever disappeared gradually, by lysis, the decrease beginning on the fourteenth and ending on the sixteenth day of the disease.

For the next ten days there was no more fever, and the child seemed to recover perfectly, though the resolution of the infiltrated parts of the lungs seemed to progress slowly. On the twenty-seventh day there was a new, sudden onset of high fever, the cause of which could clearly be seen already on the following day; there was a distinct pneumonic invasion in the lower lobe of the right side. In the area below the right scapula there was moderate dulness, distinct tubular breathing, broncho- and ægophony, and marked increase of the vocal fremitus. The new pneumonic attack terminated in a crisis on the fifth day, or the thirty-second of the entire disease.

For the next three following days the child seemed to be in a normal condition. On the fourth day, however, a new morbid status appeared. The child became restless, complained of pain, repeating often "here," while pointing to a spot in the right hypochondrium; was afraid of being moved. The tongue became coated again and the body was often covered with perspiration. The temperature rose to 105° in the afternoon, while there was a full remission in the morning. There was a moderate swelling of the spleen, and the liver could be felt protruding below the ribs. The former dulness below the right scapula disappeared in the upper part of the area while it turned into flatness in the lower part of it. Here neither respiratory murmurs nor the vocal fremitus could be noticed.

On the sixth day of the new state (forty-second of the entire disease) I made an exploratory puncture in the eighth intercostal space and an odorless pus was obtained. The diagnosis of empyema thus being apparently well assured, surgical treatment was resorted to. On the following day (the forty-third of the entire disease), after making a long incision over the eighth rib, beginning at the median axillary line and extending backward, I removed a piece of the rib—about an inch and a half. Before opening the pleura I made another exploratory puncture and withdrew pus again. After opening the pleura, however, I was greatly surprised to find very little pus in the pleural cavity, the entire amount being hardly more than half a teaspoonful. The aperture was wide enough to see distinctly the perfectly motionless diaphragm bulging high up into the thoracic cavity. The exploration with the finger revealed that the lung was not collapsed, the diaphragmatic side of the lower lobe apparently being still somewhat consolidated; there were no adhesions or encapsulated empyema; but distinct fluctuation could be felt through the diaphragm. In a word, I had before me a sub-phrenic abscess.

After a close examination, I discovered in the diaphragm a very small perforation, not larger than a pin-head, leading into the abscess. The opening was close to the ninth rib in the posterior axillary line. Apparently through this perforation a few drops of matter found their way into the pleural cavity. I then dilated this opening, introduced a thick rubber tube into the abscess cavity, and by massaging the diaphragm succeeded in removing the entire pus through the tube, thus avoiding the invasion of the matter into the pleural cavity. By digital examination of the abscess cavity I ascertained that there were apparently no pus-containing pockets in the neighborhood, and that the surface of the liver was perfectly smooth. The abscess cavity seemed to be closed on all sides by firm adhesions. I then washed out the pleural as well as the abscess cavity, introduced drainage-tubes in both, and applied a bandage in the usual manner. No more matter came through either of the tubes. On the third day after the operation I removed the tube from the pleural cavity, and on the fifth day the opening leading into it was perfectly closed and there was distinct vesicular breathing with no signs of pneumothorax. The drainage-tube below the

diaphragm I did not remove for nearly three weeks, fearing there might be, after all, another abscess hidden in the neighborhood of the first one. The reason for this suspicion was the continuation of the fever.

In the first three days after the operation the fever became even continual in character, with 104° in the morning. On the fourth day the former hectic state reappeared, 105° in the evening and full remission in the morning. No physical signs whatsoever indicated the presence of another gathering, the pain disappeared; the liver returned to its normal place, and only the spleen still remained somewhat enlarged.

Remembering my experience with some obscure cases of persistent hectic fever after pneumonia, which yielded abruptly to large doses of quinine, I resorted finally also in the present case to this remedy. The result was surprising. After administering for two days fifteen grains of quinine a day, the fever disappeared and the child recovered rapidly. (I hardly need to say that there is a possibility that the rapid recovery was merely coincidental to the administration of quinine. In the case of subphrenic abscess operated upon successfully by Monastyrski[1] the fever continued also for some time, but then disappeared without any medication.) Twenty-two days after the operation the wound was healed and the child was henceforth in every respect in a normal condition. The entire disease lasted sixty-five days.

Let us recapitulate briefly. The disease began with a croupous pneumonia which was limited to the right apex. After a slow defervescence and a protracted resolution the pneumonic infection befell also the lower lobe of the same side, which had a short duration and terminated in a crisis. There can be no doubt as to the pneumonic nature of the second attack. The sudden rise, the continuity and the critical fall of the fever, the moderate dulness, the bronchial breathing, and the increased vocal fremitus, all speak in favor of pneumonia. Moreover, by the digital exploration I felt the remainder of the consolidation within the lower lobe. Both attacks may be well termed *migratory pneumonia.* A few days after the termination of the last pneumonic attack a morbid state gradually made its appearance which had all the characteristics of a meta-pneumonic empyema. The operation revealed that all the physical and rational symptoms were due to a subphrenic abscess, while the pleura was intact.

We see here a subphrenic abscess following closely croupous pneumonia in a patient who at no time has shown any abdominal symptoms. There can be hardly any doubt that the preceding pneumonia

[1] Monastyrski: St. Petersburger med. Wochenschrift, 1889, p. 53.

was the cause of the consecutive subphrenic abscess. The only other possible explanation would be to say that the immediate development of the abscess after pneumonia was only a matter of accident, and that the real primary cause was unknown. This is far-fetched and unreasonable, and we might apply such objections to all kinds of sure causes established by the inductive method. In my opinion there is practically only one possible explanation, and that is that the preceding pneumonia was the cause of the consecutive abscess.

The question arises whether my observation presents a type, or the case was only an isolated and accidental one. A close examination of the literature brought to light at least one other similar case. It was reported by Gaehde[1] in 1880, almost simultaneously with the publication of Leyden; it has escaped the general notice. Here is the case in brief.

In a man of twenty-eight, pneumonia of the lower lobe of the right side terminated in a crisis. A few days after, exquisite symptoms of empyema made their appearance in the same side. Paracentesis with a resection of a part of the sixth rib was performed, but only a small quantity of pus escaped. The diagnosis was made that there might be an encircled empyema below the opening, and a spontaneous evacuation into the upper pocket was expected. In the days following, a considerable discharge of matter, indeed, took place and the patient was recovering satisfactorily when he died suddenly. It was one of those obscure, accidental deaths occurring now and then in the course of pleurisy. The autopsy revealed the surprising fact that the cut was made right through the diaphragm and the pus was coming from below it. The type of subphrenic abscess apparently was yet unknown to the author, and he speaks indefinitely of perihepatic abscess. Here, then, we have a distinct case of subphrenic abscess following pneumonia, and here also the pneumonia was apparently the cause of the consecutive abscess.

I met in the literature with another case of subphrenic abscess following pneumonia, but the causal connection between the two is less sure. The case was reported by Jahn,[2] in 1888. A soldier had

[1] F. Gahede: Ein Fall von Pneumonie mit nachfolgendem Empyem. Operation—Perihepatischer Abscess, plötzlicher Tod. Berliner klin. Wochenschrift. 1880, p. 134.

[2] E. Jahn: Subphrenischer Abscess bie rechtsseitiger Lungenentzündung, etc. Deutsche med. Wochenschrift, 1888, p. 1042.

croupous pneumonia of the lower lobe and the defervescence took place on the sixth day. Three weeks later, while still in the hospital, a new sickness began with a chill in the onset and there was pain in the right side; spleen and liver were enlarged and a continued fever lasted twelve days. The diagnosis was typhoid. A few days after defervescing, continued fever began again, but lasted only two days, when it turned into a prolonged remittent and intermittent type. At the end of the third month thoracocentesis in the ninth intercostal space was performed. The pleural cavity was found to be empty and smooth, the diaphragm motionless, and beneath it an abscess. It was evacuated and the patient recovered within six weeks. Jahn himself is not very sure about the diagnosis of typhoid, but he is loath to believe that the abscess was originated by the preceding pneumonia, on account of the absence of any kind of pleurisy. We shall soon see that this latter point is rather favorable to the development of a subphrenic abscess, and I am, indeed, inclined to believe that in this case also the abscess was caused by the preceding pneumonia, and that the second attack of continued fever was not typhoid, but the first stage of the developing subphrenic empyema; the pain in the side and the enlarged liver rather favor this theory. At the same time I must say that another hypothesis is also admissible, viz.: that the convalescing patient became, indeed, infected with typhoid by coming in contact with typhoid patients in the hospital, and that the typhoid then might have been the cause of the abscess.

Leaving this last case, as a doubtful one, out of consideration, we have then at least two cases of subphrenic abscess which most certainly were caused by pneumonia. Are those two cases actually the only ones? I am inclined to doubt this the more, as an analysis of these cases will show that even they were discovered only accidentally. If we take first the case of Gaehde, we see that the patient was operated upon for empyema, and that the real state was not recognized even at the operation. If the patient had not died accidentally he might have recovered, as there was a wide opening in the diaphragm and the pus had a free outlet. The favorable condition of the patient justified, indeed, the hope of the surgeons for his recovery. Now if this patient had recovered nobody would have ever detected that it was not a case of empyema! Similar circumstances we meet with in my own case. The diagnosis of empyema was well

founded and I operated for it pretty early. I found a small perforation of the diaphragm and only a few drops of pus within the pleural cavity. If I had waited longer with the operation, as is sometimes advised, at least in cases of meta-pneumonic empyemata, the perforation would have meanwhile probably become large, and there would have been a sufficient quantity of matter within the pleural cavity to have left undisturbed my original belief that I was, indeed, dealing with empyema. Nevertheless the little patient would even then have stood a good chance of recovery, since the ample perforation in the diaphragm would have permitted the abscess to empty its entire contents into the pleural cavity, and from there the pus would have made its further escape through the wide wound. Thus in my case also a recovery could have happened without my knowing that it was in fact not empyema, but rather a subphrenic abscess.

But if these cases have been discovered only by mere accidents how can we insist upon it that those are actually the only ones that ever occurred! On the contrary, it seems very probable to me that many cases of subphrenic abscess after pneumonia have been mistaken for meta-pneumonic empyema. There is no symptom capable to serve as a reliable means for differential diagnosis between subphrenic abscess and meta-pneumonic empyema; but even if there would have been such a reliable guide, who has ever seriously taken the possibility of a subphrenic abscess into consideration while studying the symptoms of meta-pneumonic empyema? Thus the want of a larger number of similar cases does not speak against the frequency of their actual occurrence, while the accidental detection of the two reported cases decidedly justify the expectation that more cases of this kind actually occur, but remain undiscovered.

By analysis of the circumstances in my own case, however, I am forced even to a still further step; I am forced to the assumption that subphrenic abscesses after pneumonia not only occur more often, but they even present a legitimate type; the abscess below the diaphragm is as much of a natural—though, may be, a rare—sequela to lobar pneumonia as is the empyema above the diaphragm. There can be no question that the subphrenic abscess in my case was caused by the preceding pneumonia. But this can only mean that the abscess below the diaphragm was caused by the pus-producing organisms which are present in pneumonic infiltrations. I did not make

any bacteriological examination of the pus in the abscess, as I was not prepared to find anything else than an ordinary meta-pneumonic empyema, the bacteriology of which has been sufficiently studied by Netter and others. The organisms of the abscess were probably the same as those usually found in meta-pneumonic empyemata, viz.: pneumococcus lanceolatus or streptococcus pyogenes. These organisms, we have to assume, passed directly from the pneumonic lesion in the lungs into the space below the diaphragm through the lymph channels of the latter, which are, according to the studies of Ludwig and Schweigger-Seydel,[1] quite wide and well shaped. The location of the pneumonia in the lower lobe close to the diaphragmatic surface was one of the favorable conditions for such a direct transmigration. And it is my belief that the absence of any pleuritic inflammation, as it was disclosed at the operation, was another point favorable to the passage of organisms through the lymph channels of the diaphragm. If the migration of the organisms from the pneumonic focus had been preceded by inflammation of any kind of the diaphragmatic pleura, the organisms would have been prevented from passing through the lymph channels, as the stomata on the thoracic side of the diaphragm would have been obliterated by fibrin. The organisms would thus have been retained on the inflamed pleuritic surface, and the result would probably have been a diaphragmatic empyema. In the case of Gaehde there is no remark as to the condition of the diaphragmatic pleura, but Jahn reports expressly that the pleura did not show any kind of pleuritic inflammation. It was just this point, as we have mentioned above, which made Jahn disbelieve that the pneumonia was the cause of the subphrenic abscess in his case; while I think just the contrary—that the absence of inflammation, at least in the diaphragmatic part of the pleura, is a necessary link between pneumonia and subphrenic abscess.

To state my opinion more precisely, I sum up as follows:

The migration and deposition of the organisms of pneumonia in the adjacent spaces is the cause of the formation of a meta-pneumonic abscess, which may then be located either above or below the diaphragm. When the pneumonia is localized near the costal or the intra-lobar surfaces of the lungs, the migration of the organisms

[1] Ludwig u. Schweigger-Seydel: Ueber das Centrum tendineum des Zwerchfells, Arbeiten der physiologischen Anstalt zu Leipzig, 1866.

results probably always or nearly always in supra-phrenic empyema. But if the pneumonic focus is located close to the diaphragmatic surface of the lungs, the result depends upon the state of the diaphragmatic pleura. If this be not inflamed and the stomata of the lymph channels of the diaphragm not occluded, the migrated organisms may find their way directly into the space below the diaphragm, and the result will be a subphrenic abscess. But if the migration was preceded by some inflammation, thus occluding the channels leading to the space below the diaphragm, the organisms will remain above the diaphragm, thus forming a supra-diaphragmatic empyema.

I have here presupposed that the organisms can easily pass through the lymph channels of the diaphragm in the direction from the thoracic to the abdominal side of it. This would seem to be in contradiction to the well-known experiments of v. Recklinghausen,[1] who observed the passage of different kinds of corpuscular elements from the abdominal cavity through the lymph channels of the diaphragm to the thoracic surface of the same, but did not succeed in observing the passage of any elements from the thoracic side to the abdominal surface of the diaphragm. Recklinghausen himself, however, explains this failure by the fact that the introduction of any kind of foreign bodies into the pleural cavity produces immediately a pleuritic inflammation, thus obturating the stomata, and he does not deny the possibility that the undisturbed stomata and lymph channels may well serve as a thoroughfare even in the direction from the thoracic to the abdominal cavity. Perhaps new experiments with micro-organisms will furnish, indeed, better results. Above all, we should not forget that in the case of the transmigration of the organisms from the lungs through the diaphragm, this latter remains, in contrast to the artificial experiments, in close contact with the diaphragmatic surface of the lungs, and the organisms may just walk over from the stomata of the lungs into the stomata of the diaphragm without coming at all in contact with any pleural surface.

Thus there are on record at least two, and perhaps three, cases of subphrenic abscess, the primary cause of which was lobar pneumonia, and it is probable that in reality more cases of that kind occur, but pass unrecognized, as meta-pneumonic empyemata. These cases

[1] v. Recklinghausen: Zur Fettresorption. Virchow's Archiv, Bd. xxvi. p. 172.

form, at any rate, a contrast to the prevailing view that the primary causes of the subphrenic abscess are always located within the abdominal cavity. Aside from this group of meta-pneumonic subphrenic empyemata, we find in the literature three more cases of subphrenic abscess, the primary cause of which is tabulated as being located above the diaphragm. In one case (Falkenheim[1]) we read that a subphrenic abscess was caused by a tuberculous cavern. But we can hardly put this abscess in line with the others. The cavern caused empyema which perforated the diaphragm, and thus produced, among other abscesses within the abdominal cavity, also an accumulation of pus between the liver and the diaphragm. In two other cases (Herrlich[2] and Nowack[3]) endocarditis is noted as the cause of the subphrenic abscess. But here the immediate cause of the subphrenic abscess was, indeed, located within the abdominal cavity, as it was in fact the abscess or the infarct of the spleen which caused the subphrenic abscess, though the abscess and infarct of the spleen in their turn were caused by the preceding endocarditis.

A case with quite a puzzling history was recently reported from the Greifswald surgical clinic.[4] The cause of the subphrenic abscess was not located in either of the body cavities. Paronychia in a boy of seventeen was treated with a radical incision, and smooth recovery followed; nineteen days after incision a chill introduced symptoms of suppurative pleurisy—the diagnosis was indeed empyema, and Helferich resected the ninth rib, but the presence of the spleen in the abscess cavity proved that the abscess was located below the diaphragm. Rapid recovery followed. The report is very short, but from the heading it is shown that Helferich considers the preceding paronychia as the primary cause of the subphrenic abscess. The connection is quite obscure, but there was, perhaps, an infarct of the spleen; there is nothing in the report to the contrary. We could then assume that endocarditis was the missing link between the paronychia and the subphrenic abscess.

While in the foregoing we discussed the occurrence of cases of subphrenic abscess preceded not by abdominal but by intra-thoracic

[1] Falkenheim: Mittheilung aus der medizinischen Klinik zu Königsberg, 1888.
[2] Herrlich: Ueber subphrenische Abscesse. Deutsche med. Wochenschrift, 1886, p. 139.
[3] Nowack: Schmidt's Jahrbücher, Bd. ccxxxii. pp. 73, 200.
[4] H. Helferich: Jahresbericht über die chirurgische Klinik der Universität Greifswald während des Etatsjahres 1889 u. 1890. Leipzig, 1892.

ailments, I shall now point out briefly such cases of empyema as are preceded exclusively by pronounced abdominal symptoms. I shall mention, in the first place, empyemata originating from gastric ulcer perforating directly into the pleural cavity. Such a case was reported recently by v. Koegerer.[1] There were all the physical symptoms of pyo-pneumothorax, with no history of lung trouble, but with a sure proof of the presence of a simple gastric ulcer. According to the prevailing view this would have been a case of pyo-pneumothorax subphrenicus. The autopsy proved that the ulcer broke directly into the pleural cavity after some adhesions had been formed between the stomach and the diaphragm; the entire air-containing abscess was above the diaphragm and not below it. There are more cases of this kind in the literature, but I shall refer only to one other, which, for the sake of historical correctness, deserves special notice. It is the case of Sturges,[2] which is quoted by Pfuhl[3] as a case of pyo-pneumothorax subphrenicus, and is one of the ten cases collected by Leyden. By reading the original article of Sturges, I found that his diagnosis was that the *source* of the pyo-pneumothorax was located in the stomach and not in the lungs, but he does not claim that the *pyothorax itself* was located below the diaphragm. If his diagnosis was correct, it was then a case like the one reported by v. Koegerer, and not a subphrenic abscess.

Aside from this kind of cases there are those empyemata which accompany or follow several acute abdominal troubles like typhoid fever, general or circumscribed peritonitis, etc. In the complications or sequelæ of these ailments, we have physical signs of effusion in the lower part of the thorax and a history of abdominal trouble. According to the view set forth by Leyden we must expect in all such cases to find a subphrenic abscess, still we find actually only empyemata. I shall add, however, that in some instances the diagnosis of empyema in these cases might be indeed incorrect. This may be illustrated by a quite recent communication from the Strassburger clinic. In the *Berliner klin. Wochenschrift* for April 10, 1893, Weintraud[4] reports the following case as typhus-empyem, *i. e.*,

[1] v. Koegerer: Pyo-pneumothorax knister et ulcere ventriculi perforanti. Präger med-Wochenschrift, 1890, No. 25.

[2] Sturges: Lancet, 1874, p. 196

[3] Pfuhl: Ein oberhalb der Leber gelegenes peritonitisches Exsudat. Berliner klin. Wochenschrift, 1872.

[4] Weintraud: Ein Fall von Typhus-Empyem. Berliner klin. Wochenschrift, 1893, No. 15.

empyema following typhoid. In a patient with a moderate typhoid some dulness in a small area in the back of the thorax was noticed which was ascribed to pulmonary hypostasis. But as the dulness on the left side did not fully disappear, even after the defervescence took place, and the patient recovered but slowly, an exploratory puncture was made in the dull area, which brought out pus containing a large number of the bacillus typhosus. Two days later alarming peritonitic symptoms set in, but disappeared after eight days' treatment with opiates. A few days later the patient recovered with astonishing rapidity. Weintraud diagnosticates the case as empyema, without any discussion, and remarks concerning the spontaneous recovery, that the evacuation of the empyema through the lungs would not have escaped observation. There is no mention of the behavior of the intestines. It seems to me that this might rather be a case of subphrenic abscess than of empyema. The preceding typhoid, the smallness of the dull area, the subsequent abrupt appearance of peritonitis without any plausible cause, then again the spontaneous and quite rapid recovery, and perhaps, even, the presence of the bacillus of Eberth in the abscess, speak in favor of subphrenic abscess following typhoid. The abscess broke first into the peritoneal cavity, and later found its way into the intestinal canal, thus affecting a spontaneous and rapid recovery. In one of the cases of Leyden the subphrenic abscess found its way out, likewise, through the intestinal canal. If Weintraud only thought of the subphrenic abscess, possibly he would have come to the same conclusion.

Aside from the theoretical interest there is a great practical importance attached to the differential diagnosis in such cases. While Weintraud, believing that his case was one of empyema and that the recovery occurred by absorption, recommends not to decide hastily for the radical operation, I, on the contrary, take his case as a proof that even the most innocent-looking abscess may suddenly break into the abdominal cavity and produce general peritonitis, of which only a very small percentage will result in recovery by emptying the entire abscess into the intestinal canal.

CASES OF SUBPHRENIC ABSCESS.

By WILLIAM OSLER, M.D.,
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THE following cases illustrate some of the forms of abscess beneath the diaphragm; three contained air and simulated pyo-pneumothorax; in two the condition was strikingly similar to empyema. The pus may be either in the cavity of the lesser peritoneum, which is commonly the case when perforation of the posterior wall of the stomach, or of the duodenum, occurs, and the abscess is then chiefly beneath the left half of the diaphragm; or it may be between the right lobe of the liver and the diaphragm, in which case the abscess is really within the general peritoneum, though usually shut off. The abscess may come from perforation of the ascending colon, or from the appendix, or from the liver itself. In the air-containing abscesses the most exquisite simulation of pneumothorax may occur on this side, as in the case which first called my attention to this condition, occurring in the practice of Dr. Gardner,[1] of Montreal, in which the signs of pneumothorax extended as high during life as the third right interspace, and in which, post mortem, the diaphragm was found at the level of the third interspace.

Case II. is of interest from the development of the air-containing abscess in consequence of the perforation of the colon and communication with a perinephritic abscess on the right side. This, too, had perforated the diaphragm and produced a pleurisy at the right base.

In Case III., on the other hand, there was, following injury to the kidney, an empyema which had perforated into the lung and the subphrenic abscess received its air supply from this source, which is somewhat unusual.

[1] Canada Medical and Surgical Journal, vol. ix.

The two cases of simple subphrenic abscess are of doubtful etiology, and are of interest chiefly from the remarkable simulation of empyema and the good results which followed operation.

Case I. is one of the few instances in which the diagnosis of pyo-pneumothorax subphrenicus was made during life, and in which recovery followed operation:

CASE I. *History of dysentery; symptoms of abscess of liver; development of a large area of tympanitic resonance in the right lower axillary region; diagnosis of pyo-pneumothorax subphrenicus; operation; recovery.*—John S., aged thirty-six, was admitted to the Johns Hopkins Hospital on January 16, 1890, complaining of fever, diarrhœa, and pain in the abdomen. There was nothing of moment in his family history. He had typhoid fever when twelve years of age. He has had gonorrhœa, but not syphilis. He has been a very hard drinker for very many years. In September, 1888, he had dysentery; not a very severe attack, as he was not laid up in bed; but the stools were frequent, and he passed blood and mucus. He has not been entirely free from intestinal trouble since, but he has been able to keep at work with but few interruptions. Latterly he has lost flesh, and within the past six weeks has become very weak and feverish. On several occasions the feet have swollen. He has had no chills; has never been jaundiced, and has never had severe pain in the region of the liver. He stopped work two weeks ago.

Condition on admission. Emaciated; weight 116 pounds; anæmic, muscles flabby; skin hot, dry, and sallow; conjunctivæ white; tongue pale, indented, and with numerous aphthous sores on dorsum and sides. Pulse 96; respiration 30; temperature 101°. Lungs are normal with the exception of a few dry crepitant râles, probably pleuritic, at the right base.

Cardiac dulness begins at the fourth rib. There is a soft systolic apex murmur. The second sound is reduplicated at base.

Liver. No prominence in hepatic region. No tenderness on pressure. Dulness begins in nipple line at fifth interspace and extends about 4 cm. below the costal margin, 15 cm. in vertical extent. The edge cannot be distinctly made out. The surface beneath the costal margin is not rough; not tender. In the median line, dulness extends 3 cm. below the tip of ensiform cartilage.

Spleen not palpable. Area of dulness not increased.

The abdomen is symmetrical, a little full, tympanitic; nowhere tender. Examination of blood negative.

Urine. Specific gravity 1019; reaction acid. Trace of albumin. No tube-casts. The stools were frequent, liquid, and contained much mucus.

From the history of the case and from the appearance of the man, abscess of the liver was suspected.

For the first ten days in the hospital the patient seemed better. The

number of stools in the day reduced. He had no chills. On several occasions he sweated heavily at night. The temperature range was from 98° to 102°.

On the 24th it was noted that "there is distinct tenderness in the right renal region, best elicited on bimanual palpation. No special fulness. No dulness in the right flank. Liver dulness is not increased in the lateral region; in the posterior axillary line it begins at the eighth rib and extends to the costal margin."

January 8. The tenderness on the right side has increased, and it is specially noticeable at the extremity of the tenth rib when pressure is made upward. There is here a distinct sense of fulness and resistance. To-day there was noticed on percussion a remarkably tympanitic and highly metallic percussion note between the ninth and eleventh rib on the right side. An exploratory puncture, in the tenth interspace, posterior axillary line, obtained a small amount of curdy, thick pus which contained altered pus cells and a few fat crystals. The following note was dictated:

In the right flank the fingers can be passed well toward kidney, with, perhaps, slight sense of increased resistance. With bimanual palpation there is certainly great resistance below costal margin, and especially below points of the tenth and eleventh ribs; here there is also marked tenderness. From behind there is distinct fulness in the infra-scapular region on the right side, and intercostal spaces are here not so well marked. There is no distinct tenderness in right lumbar space behind. Liver dulness in mid-sternal line extends three fingers' breadth (5 cm.); in nipple line from lower margin of the fifth to costal border. In mid-axillary line there is a pulmonary note to lower margin of sixth. In mid-axillary line there is dulness for a finger's breadth on the seventh rib, and then there is the most extreme metallic tympany extending from exactly the seventh interspace to upper margin of eleventh, where it passes on insensibly into bowel tympany. There does appear, however, to be a slightly dull note before bowel tympany is reached. Anteriorly the metallic tympany extends to within 4 cm. of nipple line. Behind it extends to posterior axillary line. When turned on side, percussion in axillary line is distinctly flatter, and there is movable dulness. Altogether tympanitic area occupies position of seventh to tenth interspaces in a line drawn at the level of ensiform cartilage. A diagnosis of a subphrenic air-containing abscess was made, and the patient was transferred to the surgical department.

On the 29th Dr. Halsted resected about one inch and a half of the tenth rib in the mid-axillary line, and removed about a litre of a thick grumous pus, which had an acid reaction and very distinct odor of vomit. The patient rallied well from the operation.

February 2. The last few days the patient has had a slight elevation of temperature. His general condition, however, is good. The tympanitic note is even more intense than before the operation and it is almost amphoric in character. It extends anteriorly as far as the nipple line, where it is only 10 cm. from the nipple line. The area is triangular in shape, the apex being

toward the sternum. It is 15 cms. in transverse diameter. The liver seems pushed far over into the left hypochondrium.

10*th*. Since the last note the patient's condition has rapidly improved. The temperature has been but slightly above normal, the sweats have stopped, the diarrhœa checked, and his appetite has become very good. The wound is dressed every day and the cavity irrigated. Dr. Halsted is now able to pass his finger far down into the flank, reaching quite to the level of the crest of the ilium. A flat tympany extends in the mid-axillary line from the lower margin of the eighth to the iliac crest.

14*th*. General condition remains excellent. The cavity has reduced very considerably and the discharge has lessened.

The improvement continued, and the patient was discharged well.

CASE II. *Tuberculous pyelo-nephritis; tuberculous colitis; perforation at splenic flexure of colon, with the formation of a perinephritic air-containing abscess; prominent tumor over tenth, eleventh, and twelfth ribs behind; incision and drainage; pulmonary tuberculosis; death; autopsy.*—In October, 1887, I saw, with Dr. R. H. Harte, of Philadelphia, a case which illustrates a somewhat unusual form of this condition. He was a young man, aged about thirty, who, as early as 1880, had passed blood and clots with the urine, and was sent to California under the impression that he had Bright's disease. He lived a pretty hard life, and had been treated for stricture of the urethra and irritable bladder. When Dr. Harte saw him in July he had lost much flesh, was very pale, but was still fairly muscular. The urine contained pus and blood; the bladder was very irritable, and micturition was very frequent.

Early in September he had chills, which were supposed to be malarial; with these the fever was high, and he sweated heavily. In the middle of October diarrhœa of an obstinate character set in. When I saw him he was pale, somewhat emaciated, with an irregular fever and occasional chills, which were evidently of a septic nature. He had profuse diarrhœa, and the stools, at times, contained small quantities of pus. The urine was very purulent. On examination of the abdomen nothing of special note was observed anteriorly. Behind, on the left side, beneath the skin, over tenth, eleventh, and twelfth ribs, there was a prominent tumor, somewhat hemispherical in outline, and nearly equal in extent to the palm of the hand. It was soft, not specially tender, and, on percussion, when he was in an erect posture or on his belly, gave a most remarkable tympanitic note. On the other hand, when he was on his left side or back the note was dull. On coughing there was a distinct impulse in the tumor. Anteriorly there was nothing to be felt on deep pressure, but there was evident thickening and pain on deep pressure in the left lumbar region. It was thought at first that this projection might possibly be hernial, though in an unlikely position. Aspiration, however, revealed the presence of pus, and it was thought to be perinephritic abscess which had communication with the bowel. On November 1st he was taken to the University Hospital, and Dr. Agnew laid open the abscess freely. There was evidently communication with the bowel, as fig-seeds were, on

several occasions, noticed in the dressing. Gradual signs of involvement of the left lung came on, and he sank and died about January 1st.

The post-mortem showed extensive old tuberculous disease of the left kidney. An abscess cavity, the size of a cocoanut, surrounded it and communicated with the colon at the splenic flexure through an opening which would admit a lead-pencil. The abscess had perforated the diaphragm and produced pleurisy at the right base. There was extensive and progressing tubercular disease of the right lung. The right kidney presented a number of small tuberculous abscesses. The bladder was thickened and contracted, and presented tuberculous ulcers. There was an abscess of the prostate which opened into the bladder. The ureters were thickened and ulcerated.

The condition has been met with following injury, as in the case next given, which was transferred to my wards from the surgical side at the University Hospital, Philadelphia:

CASE III. *Injury to arm and back; hæmaturia; amputation of arm; erysipelas; three weeks after accident signs of inflammation at the left base; development of a pyo-pneumothorax; expectoration of fetid pus; septic fever; asthenia; death; autopsy.*—William S., aged twenty-four years, was admitted to the surgical wards of the University Hospital on November 13, 1885, having fallen under the wheels of an engine. The left arm was crushed, and he had a deep scalp wound. The arm was amputated at the upper third. For a week he had hæmaturia, and he complained of a pain in his left side. Subsequently erysipelas developed in both arm and face. About three weeks after admission signs of inflammation appeared in the left infra-scapular region, indicated by a rise of temperature, dulness, and feeble, blowing breathing, and he was transferred to the medical ward. The stump at this time had almost healed. Examination of the chest revealed a circumscribed dulness at the left base, extending nearly as high as the angle of the scapula, and, laterally, to the mid-axillary line. Tactile fremitus was diminished; on auscultation, feeble, blowing breathing, and on deep inspiration, râles. Slight cough; very little expectoration. A septic pleurisy was suspected. The condition remained practically unchanged for several weeks, during which there was irregular septic fever. He complained at times of pain in the ilium and left side, particularly when he drew a deep breath. He soon began to spit up fetid pus, and in twenty-four hours brought up several ounces. It was concluded that a localized empyema had perforated the lung. On examination, tympanitic resonance, amphoric breathing, and metallic râles were found low down in the postero-lateral region, beneath the eighth, ninth, tenth, and eleventh ribs, indicating pneumothorax.

The autopsy showed the existence of a large abscess behind the left kidney and descending colon, extending from the diaphragm to the crest of the ilium. The chief part of the abscess lay above the kidney, beneath the ribs, and in this region there was a distinct cavity, partially occupied by dirty-brown pus, similar to that which the patient had expectorated during the last two

days of his life. Part of the diaphragm was in a sloughy condition, and two orifices, through each of which the point of the index finger could be passed, communicated directly with an abscess cavity in the lower lobe of the left lung. The pleural membrane of this part was greatly thickened, and there was a small localized empyema between the layers. There were areas of recent broncho-pneumonia throughout the other lobe. The left kidney was small, and presented at its upper part a distinct cicatrix, to which the capsule and adjacent tissues were strongly adherent.

The sequence of events in this case was, probably, as follows: Wound of kidney with bruising of tissue in lumbar region; subphrenic abscess; localized empyema, probably from contiguity with subphrenic abscess; perforation of diaphragm and lung, with discharge of pus; development of a subphrenic air-containing cavity which gave, in the lower and lateral aspects of the left side, the signs of pneumothorax.

I regarded this case, when admitted to my wards, as one of septic pleurisy, passing on to empyema and perforation of the lung. The physical signs of pneumothorax were of the most characteristic kind, and I must confess that it never once occurred to me that the air-containing cavity was below, not above the diaphragm.

CASE IV. *Acute illness; signs of empyema; operation; pleura free; evacuation of large subphrenic abscess.*—John M., aged twenty-four, fireman, admitted April 30, 1892, complaining of pain in the right side of the chest. Nothing of any note in the family history. The patient had measles when young, otherwise has been remarkably healthy. Denies excess in alcohol; admits gonorrhœa, but has never had syphilis. His bowels have been regular; he has had no abdominal pains. The present illness began about a week ago with headache, loss of appetite. He kept at work until two days ago, when the pain became very severe in the right side of the thorax, and was much aggravated by coughing and during a deep breath. He is positive that there was no chill, but he has had one or two heavy sweats. For three days his bowels have been loose, and he has had from five to ten stools a day, but has not noticed any blood.

On admission, temperature 104°. He is a large, well-built, well-nourished man; lies upon the left side. Lips and mucous membranes of a good color; the cheeks are flushed; tongue has a whitish fur. Pulse is 92, regular in force and rhythm; respirations shallow, 36. The thorax is well formed; the left side moves more than the right.

Percussion. Resonance normal on the left side. On the right side the patient winces on percussion below the fourth rib. The flatness begins at the upper border of the sixth rib in mammary line. Behind the resonance

is defective at the right base and in the lower axillary region, and possibly there the line of dulness in front varies slightly with the position. The fremitus is diminished over the flat area.

Auscultation is everywhere clear in the left chest and in the upper part of the right, but in the flat area the respiratory and voice sounds are diminished in intensity, and in the lower mammary region there are a few dry râles. The condition of the heart is normal.

The abdomen is full; the walls are tense. There was no tenderness; no glandular enlargement; and the only point of special moment was the distinct increase in the size of the spleen, the edge of which could be easily felt at the costal margin. The blood was negative as regards the malarial plasmodia. There was marked leucocytosis—18,000 white corpuscles per c.cm.

The urine presented a trace of albumin, was dark amber-colored, acid; specific gravity 1020.

The patient had a slight cough, with a muco-purulent, slightly bloody expectoration, in which there were numerous cocci, some encapsulated. It was evident during the first week in the hospital that the patient was very ill. Every day the temperature rose to between 103° and 104°, occasionally reaching 105°, and once 106°. The pulse range was from 100 to 120. He had at times heavy sweats, and on the 2d of May he had two severe chills, in one of which the temperature rose to 106.2°. The dulness at the right base persisted, beginning in the back about the ninth rib, and in front in the recumbent posture at the fifth rib. There seemed very little doubt to Dr. Thayer, under whose care the case came, that there was pus in the pleura, and an aspirating needle was inserted, but without obtaining any pus.

During the second week the patient emaciated rapidly; the fever persisted until the eighth, and then fell to normal, the range being between 97° and 99°. The spleen remained large; there were definite sweats, but he seemed altogether better. On May 9th the blood count showed a diminution in the number of leucocytes—13,000 per c.cm. The temperature remained low, and the patient seemed to be somewhat better until the 15th, when "it rose to nearly 105°, and the pain in the side has been worse ever since he sat up with the bed-rest two days ago. Yesterday it became very intense. The physical signs have scarcely changed. There is still flatness from the fourth rib, and behind from just below the angle of the scapula. The apex-beat of the heart can now be accurately localized, and is in the fourth interspace 1.5 cm. outside the nipple. The respiratory sounds are feeble and distant."

On the 16th the patient was again aspirated, and this time pus was found which was a little stained, and contained the staphylococci and micrococcus tetragenus. Shortly after the aspiration the patient was seized with a fit of coughing and began to expectorate a quantity of reddish-brown, anchovy-sauce-like sputa, which was examined for amœba, without finding any. It was then determined to transfer the patient to the surgical side for operation. Before the transfer the following careful note was made: "The patient is propped up in bed; the right side of the chest seems a trifle fuller than the

left, the upper part looking more nearly equal. Motion is defective in the lower right front. On the right side flatness begins in the upper sternal line in the third space, at the upper border of the fourth in the nipple line, and at the fourth space in the mid-axillary line. Posterior flatness begins at the angle of the scapula. In the erect posture the upper limit of dulness in front appears to move slightly. On the right side the percussion is clear. Respirations are clear at the apex in front, but diminish greatly in intensity over the flat areas, and is of a distant tubular character. The voice sounds have a somewhat nasal quality. The vocal fremitus is only just perceptible. In the infra-scapular regions the inspiration has a more distinctly tubular character, and there is very distinct ægophony. The liver does not appear enlarged downward, and the border is not palpable."

The case was thought to be probably empyema, though the possibility of an hepatic or a subphrenic abscess had been considered.

The following is an abstract of the operation by Dr. Halsted:

The eighth rib on the right side was exposed by an incision from the axillary line to the nipple line; a portion of the rib, 5 cm. in length, was excised. It was found that the costal and diaphragmatic pleural surfaces were adherent. An incision made through these and the diaphragm opened at once into a large subphrenic abscess, which was freely evacuated and packed with iodoform gauze. The patient reacted well from the operation, and made practically an uneventful recovery. The discharge of pus gradually diminished, and he had fever only on two days. He had a chill on the 30th of May and on the 3d of June, after which he had no further fever. His weight rose from 129 to 156 pounds, and he was discharged August 15th with only a small sinus remaining.

CASE V. *Acute rheumatism; during convalescence signs of large empyema; operation; 100 c.c. clear serum in pleura; evacuation of large subphrenic abscess; recovery.* —Thomas F. M., aged fourteen, schoolboy, admitted August 3, 1892, complaining of pain in the shoulders and in the stomach. His family history is good. He has had measles once, and diphtheria twice, but has been until quite lately healthy and strong. The present illness began three months ago with pain and swelling, at first in the ankles and knees, and subsequently in the hips and other joints. Evidently from his account he had a pretty sharp and somewhat protracted attack of acute rheumatism. He had been convalescent and doing very well until two weeks ago, when he had pain in the right side, cough, and slight expectoration. For at least two weeks he has had some shortness of breath, which lately has increased very much. He has had no diarrhœa; the bowels have been regular, the appetite fair. He has had chilly feelings, but no definite rigors; has at times been feverish, and has sweated freely at night. He states that he has lost about twenty-five pounds since the beginning of his illness.

On admission, the patient was emaciated, pale, propped up in bed, the pulse at 124, regular; the temperature 100°, rose within a few hours to 103°. The respirations were 28.

Thorax. Prominent on the right side, which does not move nearly so much as the left, and there is distinct prominence in the fourth and fifth right spaces under the nipple.

Percussion on the right side gives a somewhat tympanitic resonance in the infra-clavicular space, gradually shading into flatness at the fourth rib, the line of dulness extending through the lower axillary region to a point just above the angle of the scapula. In the erect posture the line of absolute flatness in front is distinctly higher. Tactile fremitus is absent in the flat regions. The respiratory sounds are everywhere clear except at these parts, where the respiratory murmur is scarcely audible. On the left side the physical examination is negative.

There is no expectoration. The apex-beat is under the fifth rib in nipple line. The first sound is loud and sharp, and the second sound at the margin of the sternum was louder than the left. On palpation there was a suggestion of a thrill at the apex region, and there was a slight echo in diastole, but no definite murmur. The abdomen presents nothing special on inspection; the liver dulness extends three fingers' breadth below the costal margin. The border is not accurately palpable, owing to the contraction of the abdominal muscles. The edge of the spleen is not palpable. The patient remained in the medical wards for five days. The temperature range was from 98° to 103.5°. He had no chills, some sweating; the pulse ranged from 110 to 130. On the 7th pus was drawn off with an aspirating needle, and the patient was transferred to the surgical side with the diagnosis of empyema. The pus was creamy-looking, but no micro-organisms were found.

An operation was performed by Dr. Finney on August 11th. About 9 cm. of the ninth rib on the right side was excised. An aspirator needle was then passed through the thickened pleura, but seemed to enter a solid mass, and nothing was obtained. On a second attempt 250 c.c. of pus were withdrawn. The pleura was then incised just above the diaphragm. No pus was found, but about 100 c.c. of clear serum. The diaphragm presented at the wound. The pleural cavity was shut off as completely as possible with strips of gauze, and the diaphragm was incised with the Paquelin knife, opening into a large pus cavity with numerous pockets. About 100 c.c. of pus were evacuated. A rubber drainage-tube was inserted into the pus cavity. The patient did remarkably well; the temperature fell; he was dressed daily; the discharge was free, and he gained in weight, and left the hospital on September 9th, still with a slight sinus.

DISCUSSION.

DR. WELCH: In the first case related by Dr. Osler I found in the pus the bacillus coli communis, which was obtained in large number in cultures. The demonstration of this bacillus is common in abscesses communicating with the stomach or intestine. It may be present in peritoneal exudates

without actual perforation of the intestine. I regard the recognition of this bacillus, often mixed with other bacteria, in pus withdrawn from the abdominal cavity, as a valuable aid in the diagnosis of abscess resulting from lesions of the alimentary tract.

The class of cases related by Dr. Meltzer must be rare. I should not be inclined to assign so decisive a rôle to the direction of the lymph current as he does in explaining the occurrence of subphrenic abscess consecutive to croupous pneumonia. Micro-organisms can make their way both with and against the lymph stream.

Dr. Fitz: I wish to say a word in agreement with Dr. Mason as to the clumsiness of the term "pyo-pneumothorax subphrenicus." It seems to me that it would be much better if we should consider this class of cases under the head of "Subphrenic Peritonitis," since this is the anatomical condition present, and it includes cases of serous peritonitis, as well as those in which pus is present. This term is not only anatomical, but is also more comprehensive than such terms as peri-hepatitis, peri-gastritis, peri-splenitis, and omental bursitis. It seems to me that by thus emphasizing the peritonitic nature of the process we are led more directly to the etiology, and also more directly to what is perhaps the best region for the treatment of this class of cases. If the relation to the thorax is considered too particularly, the tendency is to operate through the thoracic wall, whereas the most favorable results are obtained by an operation below the costal cartilages. An illustration of the method of etiology which Dr. Meltzer has referred to occurred last winter in my wards at the Massachusetts Hospital. An Indian who had been exposed on the plains was seized with some inflammatory disturbance, the nature of which was uncertain, but was evidently intra-thoracic. After several weeks, even months, of dyspnœa and light febrile condition, he presented himself for treatment, with signs which were conspicuously those of a pleural effusion. He was tapped, and a considerable quantity of serous fluid removed, but his condition did not improve. He was then transferred to the surgical side, where Dr. Elliot opened the chest. Finding very little fluid in the thoracic cavity, he passed the knife through a resistant structure, either lung or diaphragm, and evacuated a considerable quantity of pus. It seems to me that this man might be classed with those cases where the primary process was on the upper side of the diaphragm.

Another point, not referred to by Dr. Mason in connection with the etiology, has been strongly presented to my mind within the past few months. This is the probable pancreatic origin of many of the cases which belong under the head of subphrenic peritonitis. These are generally described as cases of pancreatic cyst, and are usually of traumatic origin. My study of this class of cases has made it appear that the so-called pancreatic cyst of traumatic origin is almost invariably one in which no cyst of the pancreas is present, but in which, on the contrary, the lesions are indicative of an inflammation of the lesser omental cavity, an omental bursitis; and

these are, furthermore, the cases which generally recover after operation. In this respect my conclusions are in harmony with those recently published by Mr. Lloyd, of England. In brief, most of the cases of so-called traumatic cyst of the pancreas are really instances of subphrenic peritonitis limited to the omental bursa, and are extremely amenable to surgical treatment.

DR. MASON: I have been much interested in the cases of Dr. Meltzer and Dr. Osler. The subject is evidently such a wide one, including abscesses from so many different causes, that it is difficult to bring it within the compass of one or two papers. The matter of disease of the pancreas, referred to by Dr. Fitz, I did not altogether overlook. In several of the cases which I read, it appeared that the disease involved the pancreas, and the abscesses were said, in some cases, to have destroyed a portion of that organ, but it occurred to me that the origin might have been in the pancreas, as in a certain number of cases this was undetermined.

THE DETECTION AND SIGNIFICANCE OF PROTEIDS IN THE URINE.

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Until within a comparatively recent period it has been considered sufficient for clinical purposes merely to determine the presence of proteid matter in the urine without regard to the special form in which it occurred. Indeed, with perhaps one or two exceptions, little or nothing definite was known of the various proteid bodies now recognized in the urine, except albumin—or serum, as it was termed—and accordingly in the older works we constantly meet with the term serinuria as applied to albuminuria in general. It is now, however, a well-established fact that in addition to serum albumin the urine may contain globulin, peptone, albumose, mucin, or fibrin. Since most, if not all, of these bodies possess distinct clinical significance of more or less value it becomes important to be able to distinguish between them when met with in the urine.

The chief clinical interest with regard to proteids in the urine still centres about serum albumin; but with our improved methods of separating and distinguishing the various proteids from each other, as well as the growing clinical importance of each, it becomes obvious that any practical discussion of this subject can no longer be considered complete which does not deal with each proteid individually. The various proteids found in the urine will therefore be considered in this paper, under appropriate divisions, as follows: (1) Albuminuria, by which alone will be meant serum albuminuria. (2) Globulinuria. (3) Peptonuria. (4) Albumosuria. (5) Fibrinuria. (6) Mucinuria.

Albuminuria.

Under this head will now be considered those conditions of the system, both local and general, which give rise to serum albumin in

the urine, either alone, or, as is more frequently the case, associated with globulin.

While albumin is undoubtedly the most common of the constituents of morbid urine, it is still a debated question if it occurs in the urine in health. It is true that occasionally the urine contains a variable, but usually small amount of albumin when the kidneys present no appreciable alterations of structure whatsoever, but, as will presently be shown, albuminuria often arises from causes entirely remote from the kidneys themselves. Albuminuria, therefore, can never be proved to be a condition of health so long as the kidneys alone are considered, and yet this would seem to be the chief, if indeed not the only condition sought to be established by the advocates of a so-called physiological albuminuria. It is certain that albumin is not always present in normal urine, and therefore it seems difficult, if not impossible, to comprehend how it can be considered a normal element of that fluid. It will be safer, therefore, always to look upon albuminuria as an index of a morbid state, either in the kidneys themselves, or in some remote part, or in the system at large. Serum albumin belongs to the class of colloid substances which do not crystallize, and under *normal* conditions do not penetrate animal membranes. It has been suggested with good reason that albumin ordinarily does not penetrate animal membranes because its molecule is greater than that of any soluble salt; and this would seem to be confirmed by the chemical expression of its very remarkable atomicity, viz., $C_{216}H_{169}N_{27}S_3O_{68}$.

It has just been stated that under *normal conditions* albumin does not penetrate animal membranes; but it is a well-established fact that alterations from the normal, either in the integrity of the membrane, in the quality of the albumin itself, or in the pressure to which they are both subjected, may result in transudation. It is more than probable that all forms of albuminuria are referable to causes corresponding essentially to one or more of the above-named alterations. In other words, albuminuria is always due either to, first, changes in the kidneys themselves which impair the integrity of the structures between the vessels and the urinary canals; second, changes in the quality of the blood which render the albumin more diffusible; third, alterations in the blood-pressure. The more common form of albuminuria, as well as the most serious in its clinical

significance, is that depending upon disturbances of the renal functions. These may be due to various causes, but most often to inflammatory and degenerative changes in the structure of the kidneys, and include the whole class of disorders commonly grouped together under the term "Bright's disease."

It is impossible always to estimate the gravity of renal changes by the quantity of albumin present in the urine. Sometimes, however, as in acute inflammatory conditions of the kidneys, when the amount of albumin in the urine ranges high—one per cent. or more—the quantity may be taken as a rough gauge of the extent of the renal lesion. The same may be said of certain degenerative changes in the kidneys, notably of amyloid disease. Under the above circumstances a marked increase or decrease in the quantity of albumin furnishes a fairly trustworthy index of the progress of the disease. These rules, however, by no means apply to all diseases of the kidneys; indeed, in certain forms of renal disease the most serious of all (interstitial nephritis), not only is the quantity of albumin in the urine small, but it may be, and often is, temporarily absent. From the albuminuria itself, therefore, without a knowledge of the special renal lesion accompanying it, we are never warranted in concluding that because the albuminuria is slight the condition upon which it depends is other than serious.

Disturbances of the circulation may bring about albuminuria without any appreciable structural changes in the kidneys themselves, provided they be not too long continued. Circulatory disturbances, in order to cause albuminuria, must extend to and include the renal vessels. In their nature they must consist of acceleration of the arterial current, or a slowing of the venous current; in either case resulting in increased blood-pressure. In albuminuria depending upon disturbances of the circulation, the quantity of albumin in the urine for the most part is small. It may be but temporary in duration, as in epileptic seizures; or it may be a permanent condition, as when depending upon organic disease of the heart.

The albuminuria of fevers owes its origin to several causes, for nearly all the known causes of albuminuria are present in some forms of acute fever. We have, for instance, accompanying changes in blood-pressure; and when long continued the febrile state is apt to induce structural changes in the renal epithelium; while alterations

in the character of the blood consequent to or entailing pyrexial states favor the transudation of albumin into the renal tubules. The special cause in certain fevers (notably infectious fevers)—micro-organisms—acts more quickly as well as more violently, rapidly inducing a high degree of albuminuria, as in the case of scarlatina.

The second class of albuminurias signify changes in the composition of the blood, which so alters the diffusibility of the albumin as to permit it to pass into the renal tubules, the renal structures remaining intact, and the blood-pressure unaltered. There no longer appears reason to doubt the hæmatogenic causes of albuminuria so ably expounded by Bamberger and Semmola. As a matter of fact, we often meet with such albuminuria in anæmic, strumous, and enfeebled individuals, when no lesion in the kidneys can be made out.

It remains to consider the significance of a form of albuminuria which is often intermittent in character, and frequently though improperly termed functional, to which Dr. Pavy's cyclic albuminuria and Dr. Moxon's albuminuria of adolescence doubtless belong. It would perhaps be more accurate to speak of these as a class of albuminurias, since undoubtedly they often owe their origin to separate causes. It is the cases belonging to this class which have given rise to so much discussion of late as to whether or not albuminuria be compatible with health. In a large percentage of these cases the albuminuria is intermittent, the intermission occurring during rest, as at night. On rising in the morning the urine is often free from albumin, but soon after rising, and especially upon exercise, the urine contains a small amount of albumin, which may or may not wear away before evening. The circumstances under which such albuminuria occurs strongly suggest that the cause is connected with changes in the vascular pressure. There may be lack of stability without loss of integrity in the renal secreting apparatus—in other words, loss of healthy tone—so that it is unable to maintain its perfect physiological balance under the varying degrees of blood-pressure brought out by exercise, and slight albuminuria results. A number of these cases occur in youths and young adults. In these cases also the albuminuria is often intermittent, although not always so. The vascular supply to the genito-urinary tract is very full in early adult life and subject to frequent periods of stress, which would favor instability of

vascular pressure. These facts favor the inference that this form of albuminuria also owes its origin to alterations of blood-pressure.

In still another considerable percentage of these cases the albuminuria is more continuous, and if an intermission occurs it is measured by weeks or months. In these cases the age of the patient is less uniform, although the albuminuria is still more common before middle age.

Now, for the most part, these cases possess certain features in common. 1st. The quantity of albumin in the urine is small, usually ranging from one-half to one- or two-tenths of one per cent. 2d. The urine either contains no tube-casts from the kidneys, or very few hyaline ones. 3d. The specific gravity of the urine is somewhat above the normal standard, as is also the quantity of urea. 4th. Evidences of cardiac and vascular changes of a permanent nature are absent. The causes of this class of albuminurias are doubtless identical with those of albuminuria before considered, but perhaps operating in milder degree. To changes in the basement membrane, alterations in the quality of the blood, or abnormal conditions of blood-pressure, must be referred all these cases, if our present doctrine of albuminuria is correct.

Instability, or lack of tone in the basement membrane may permit a slight transudation of albumin into the renal glomerule when no perceptible renal lesion is present. The defect being slight, probably no greater locally than generally or systemically, recovery is the rule under favorable circumstances, although probably a few of these cases in time terminate in serious renal defect.

Alterations in the quality of the blood, which have not markedly impaired the general health, may yet permit of slight transudation of albumin, and indeed often upon superficial examination albuminuria seems to be almost the only index of this condition. These are perhaps the least serious of all the so-called functional forms of albuminuria. There is probably no special renal defect in such cases; the deficiency is systemic or general; and so long as it continues slight, albuminuria continues without damage to the kidneys, as, in one of the writer's cases, for ten years.

Alterations of blood-pressure in the renal system must readily disturb the normal balance of its filtering mechanism, rendering transudation of albumin possible under increased pressure. When,

therefore, the heart is powerfully called upon, albuminuria is frequently noted as a result, as in the case of soldiers on a heavy march and pedestrians attempting unusual feats in walking. Instability or over-taxation of the nerve centres leads to the same results through disturbance of the vasomotor apparatus, and accordingly slight albuminuria is frequently noted as the result of mental over-work, as has frequently been observed in the cases of students actively preparing for literary examinations. This form of albuminuria usually subsides with the cause, provided the latter be not too long continued, in which case it may ultimately lead to structural change in the kidneys.

It will be seen from the foregoing considerations that albuminuria is a symptom of the most variable clinical significance, and therefore in itself it should never be accepted as proof of the existence of renal disease. As has been truthfully said, "this was the error of former times." It can only be positively asserted that albuminuria is the result of renal change when it is accompanied by products in the urine which themselves are the products of these changes, such as casts, epithelium, etc. On the other hand, it must be remembered that albumin in notable quantity is never present in healthy urine, and therefore albuminuria must always be accepted as an evidence of an existing abnormal state, either locally or generally, the gravity of which must be determined by the accompanying symptoms.

The writer holds that so-called functional albuminuria forms no exception to the above rule, inasmuch as he has never met with a case of albuminuria which did not present more or less evidence of departure from the normal balance of perfect health, either locally or generally.

Detection of Albumin.—Our present number of qualitative tests for albumin in the urine is large, so much so that it has been suggested that some of them might be dispensed with in the interests of practical clinical work. It should be remembered, however, that the more accurate methods of the present demand more tests; moreover, a perfect test for albumin (serum) remains as yet to be discovered, and, therefore, in searching for albumin accurate results are only to be reached in some cases through confirmative observations with two or more tests.

Among the qualitative tests for albumin may be mentioned:

boiling, first suggested by Contugno; nitric acid (Heller); potassio-mercuric iodide (Tanret); ferrocyanide of potassium, picric acid (Johnson); sodium tungstate (Oliver); acidulated brine (Roberts); phenic acetic acid (Millard); metaphosphoric acid (Heidenlang); chloride of mercury and sodium (Fürbringer).

In searching for albumin in the urine the writer proceeds by first employing the mercuric test for purely negative purposes, since its wide range and great sensitiveness peculiarly fit it for such purpose. If no reaction be obtained with this test it is certain that not only is the urine absolutely free from albumin, but also from all proteids, and therefore no further search is necessary.

Having obtained a distinct reaction from the mercuric-iodide test, we next proceed to prove that the reaction is, or is not, albuminous. One of the quickest, most ready, as well as trustworthy methods is by appeal to the ferrocyanic test. This test possesses the advantage over all other tests, boiling included, of precipitating all modifications of albumin—acid and alkaline; while it gives no reaction with phosphates, urates, peptone, vegetable alkaloids, or the pinic acids. It further recommends itself for rapid clinical work for the reasons that it consumes the least time in application, requires the fewest precautions, and is the least subject to error of all the tests for albumin in the urine; while in point of delicacy it is at least equal to heat or nitric acid in whatever form applied.

Doubtless the older clinicians, if for no other reason than habit, would appeal to heat and acidulation as the time-honored and most certain method in cases of doubt. With proper precautions, heat and acidulation is one of the most trustworthy methods of detecting albumin in the urine; but in point of fact, it takes more time and requires more precautions in manipulation than any other test in use. The errors liable to creep into this method are so well known that it is only necessary to refer to them. Thus, if there be but little albumin present, and the acid be in excess, the albumin may combine with the acid, forming a soluble acid albumin, which is not precipitated by heat. If, on the other hand, the acid be insufficient to distinctly acidify the urine, and if the phosphates be in excess, a portion only of the basic phosphates may be acidified, while the albumin may combine with the remainder, forming a soluble alkaline albuminate, which is not precipitated by heat. Again, if the urine contain

much pinic or pimaric acid, as sometimes occurs after the use of certain resins, as cubeb or copaiba, they may be precipitated by heat and be taken for albumin. All these sources of error are avoided by the use of the ferrocyanic test.

The great source of error in searching for albumin with most, if not all, of the newer tests is the mucin reaction, because most of these tests require acidification of the urine with a vegetable acid. Now, vegetable acids precipitate the mucin of the urine, especially if in excess, and the reagent without exception greatly intensifies this mucin reaction; so that it matters not, even though the urine be first acidified with the vegetable acid, and indeed even filtered afterward, the reagent will with certainty cause a perceptible reaction if mucin has been present, which reaction may not be albuminous at all. The reagents in use which intensify the mucin reaction after acidulation with a vegetable acid include the potassio-mercuric iodide solution, picric acid, sodium tungstate, phenic acetic acid, metaphosphoric acid, acidulated brine, chloride of mercury and sodium, and the ferrocyanic solution.

Heat possesses here an advantage over all the tests named, if properly applied, because boiling will not precipitate mucin. In order, then, to eliminate the possible source of error through the mucin reaction in applying the heat test the method of Sir William Roberts is probably the most trustworthy; certainly it is very delicate. If the urine be not acid it is treated with acetic acid, drop by drop, until distinct acid reaction is obtained; or if already acid, one drop of acetic acid is added and the upper inch only of the urine is boiled, leaving the lower stratum unboiled for contrast. Mucin will not be coagulated by this method, while very delicate traces of albumin will be brought to view, although I am not prepared to indorse Sir William Roberts's statement that this method will bring to light as delicate traces of albumin as any known test.

GLOBULINURIA.

Globulinuria is nearly always associated with albuminuria, and indeed globulin may greatly exceed the amount of albumin present in some cases, notwithstanding the proportion of globulin in the blood is only 1 to serum albumin 1.5. Globulin is said to be a

more diffusible form of proteid than albumin, and this, if true, would account for its frequent proportional excess in albuminuria. But globulinuria very rarely—almost never—occurs independent of serum albumin, and this fact would seem to negative the view of its greater diffusibility. Globulin is insoluble in water, but it dissolves in water if the latter be charged with oxygen. It is also soluble in dilute neutral saline solutions. Globulin is precipitated from its solutions by heat at 90° C., by carbonic acid gas, and by alcohol.

Clinical Significance.—From the fact already stated that globulin is nearly always associated with albumin in the urine, its general significance is nearly identical with that of albuminuria. In a few cases, however, it would seem to imply a special significance. Thus globulin is observed in unusual quantities in catarrhal inflammation of the bladder, acute nephritis, and in amyloid degeneration of the kidneys. The same is said to be the case in albuminuria associated with digestion disorders. On the other hand, in chronic Bright's disease globulin is said to be present only in small amount, and even at times absent.

Detection.—This may be effected by rendering the urine alkaline and after standing for an hour filtering out the precipitated phosphates. Then by adding an equal volume of saturated solution of ammonium sulphate the globulin will be precipitated. If the quantity of globulin present is large, the more rapid and simple method of Roberts may be practised.

PEPTONURIA.

Peptone is a proteid best known as the final product of gastric and pancreatic digestion. It is also a frequent product of retrogressive changes in albuminoids of the tissues, as well as of the corpuscular elements of the blood, and as such it assumes great importance in its clinical relations. Peptone is absent from healthy blood and normal urine; but most of the organs in health hold it in small amounts. As shown by Hoffmeister, it is a constant constituent of pus. The frequent discovery of peptone in the urine has of late led to much study with the object of determining its clinical relationship. The causes of peptonuria are evidently altogether different from

those of albuminuria; since neither nephritis, circulatory disturbances, nor anæmia seem capable of inducing it.

Generally speaking, peptonuria seems to owe its origin to retrogressive changes in the albuminoids of the organism. We, therefore, meet with it as a result of two sets of causes—general and local. Among the causes operating in a general way may be mentioned scurvy, typhus, diphtheria, tertiary syphilis, smallpox, and phosphorus poisoning, indicating very clearly that the cause lies in extensive destruction of the blood corpuscles.

The local, sometimes termed the pyogenic, causes seem to be connected with resorption of exudations of a purulent nature, so situated as to favor the products of disorganization—the peptone constituent of the leucocytes—being absorbed into the circulation, from whence it is eliminated by the kidneys. This form of peptonuria is met with in the declining stage of pneumonia, in purulent pleuritis, suppurating tuberculosis, chronic bronchial catarrh, psoas abscess, purulent meningitis, and acute articular rheumatism. In acute inflammatory diseases the appearance of peptone in the urine may be taken as an evidence that suppurative changes have been established, other known causes of peptonuria being first excluded.

Jaksch insists that as a means of distinguishing between tubercular and epidemic cerebro-spinal meningitis, peptonuria is of crucial significance, being absent in the former and characteristic of the the latter. In such cases, however, ulcerative changes in the lungs must be excluded to render this sign trustworthy. In like manner peptonuria, appearing as it usually does in septicæmia, may serve to distinguish it from latent disseminated sarcoma when, as often happens, the clinical symptoms are very similar. In short, Maixner has formulated the law that peptone is always present in the urine when pus corpuscles are forming in the organism; and for the most part in morbid conditions in which peptonuria has been noted, suppurative changes were probably also present somewhere

In addition to the pyogenic causes, peptonuria is also known to arise from a few other sources. Thus it is almost invariably associated with cancer of the liver, and this fact has led Pecancowski to the conclusion that the liver in health is concerned in the conversion of peptone into albumin.

Maixner has shown that in ulceration of the intestines the peptic

products of the stomach may pass directly into the blood through the ulcerated surfaces, and give rise to peptonuria. Finally we have puerperal peptonuria, Fischel having shown that peptone is a normal constituent of the urine in the puerperal condition.

Detection.—If the urine give a precipitate with the mercuric iodide test, but no precipitate upon boiling and acidulation, no precipitate with nitric acid and no precipitate on adding ammonium sulphate to saturation, peptone is the only proteid present.

ALBUMOSURIA.

Albumose, propeptone, and hemi-albumose are the ordinary names applied to a proteid which is best known as an intermediate product in the conversion of albumin into peptone in the course of gastric and pancreatic digestion.

Albumose, like peptone, is found in pus, but, unlike peptone, it is also present in the blood, most notably so during digestion. It has been found in the urine but comparatively few times, first by Bence Jones in a case of mollities ossium, and in a like case soon after by Kuhne. Virchow has found it in the medulla of bones in the same cases, while Fleischer found it in the medulla of normal bone. Senator found it in the urine in a number of cases, viz.: tertiary syphilis, hemiplegia, double pneumonia, diphtheria, carcinoma, and muscular atrophy.

The clinical significance of albumosuria, so far as our present knowledge extends, is very indefinite, so that practical conclusions in connection with its presence in the urine are altogether lacking; in the few diseases in which it has been found in the urine, its presence has subsequently been found very inconstant.

MUCINURIA.

Mucin is closely related to albumin, but differs from it in containing no sulphur. It is the essential constituent of mucus and therefore is present in greater or less proportion in all urines. It is non-coaguable by heat, soluble in alkalies and strong mineral acids. It is precipitated by alcohol and organic acids, as well as by dilute mineral acids.

Mucin occurs in excess in the urine in catarrhal inflammations of the urinary passages, more especially of the bladder. In urethritis, cystitis, and pyelitis the mucin in the urine is often very excessive, forming numerous ropy, tenacious strings, and it may even settle in a jelly-like mass.

Irritation of the urinary passages without inflammation or the formation of pus, often causes a notable increase of mucin in the urine. An increase is often noted also in very acute febrile conditions, as pneumonia, pleuritis, typhoid fever, pulmonary and intestinal catarrh, meningitis, and acute delirium. It is especially significant, as Reissner pointed out, that in the beginning of the febrile state, mucin often appears alone in the urine; a few days later albumin is often found; the latter usually disappears after a longer or shorter time, while the mucin continues a few days longer. Cases may be considered rare in which pronounced mucinuria persists for many days without the appearance of albuminuria, in acute pyrexial conditions. These facts should especially be borne in mind in cases of scarlatina, since the appearance of notable quantities of mucin in the urine in such cases serves to place the physician upon his guard against the approach of a serious form of nephritis.

Since the differentiation between mucin and albumin has already been dwelt upon, the detection of mucin in the urine need not detain us here.

FIBRINURIA.

Fibrin may appear in the urine from various causes, either in solution or in coagulated flakes or masses. Fibrin in the urine forms the basis of the so-called coagulable urine, which, upon standing some time, forms the fibrinous coagula. The quantity of fibrin present in the urine determines the extent of coagulation; sometimes only a sticky sediment forms at the bottom of the vessel; more rarely coagulation involves the whole volume of the urine, converting it into a sticky gelatinous mass. This form of fibrinuria is seldom met with in the United States, but it occurs frequently as a special form of disease in Bengal and the Isle of France.

Fibrinuria as it occurs with us uniformly indicates that an exudation of fibrinous fluid—blood plasma, in other words—has gained access to some part of the urinary tract. In most cases it comes from the

kidneys, although it may result from intense inflammation of the lower urinary passages. It is often associated with hemorrhages into the urinary tract, and it has been noted quite frequently in cases of villous tumors of the bladder. Finally, fibrin is found in the urine in cases of chyluria. It is important to distinguish between fibrinuria and those cases of pyuria in which large quantities of pus are present in highly alkaline urine. In chronic catarrhal cystitis, more especially of obstructive origin, the carbonate of ammonium arising from decomposition of the urine, forms with pus a gelatinous sticky mass which may be readily mistaken for fibrin coagulum. Such a urine, however, is thinned by the addition of water, and, moreover, if treated with acetic acid, a white precipitate falls consisting of alkali albuminate.

Detection.—The coagulum should be separated by filtration and washed with water, when it will show the following characteristics: It does not dissolve in water and dilute saline solutions; it swells up in one per cent. solutions of hydrochloric acid, but is only dissolved when pepsin is added. Practically if the coagula are insoluble in dilute alkalies, and in five to ten per cent. solutions of sodium chloride, they may be regarded as fibrin.

COFFEE-DRINKING AS A FREQUENT CAUSE OF DISEASE.

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THE fact that coffee has come to be greatly prized as a beverage, and to be nearly indispensable to many people, is, if there were no other evidence, sufficient proof that it powerfully influences the nervous system. It is a stimulant to the nerve centres, and, taken in moderation as an habitual part of the daily dietary it probably, to most adult persons, does no harm. Indeed, a proportion of such people can take it in moderation with apparent decided benefit to digestion, and to the regularity of alvine evacuations, as well as to the capacity for bodily and mental work. Even large quantities of it daily seem in some persons to cause no unpleasant symptoms whatever, and hardly any symptoms of any sort. In some, on the other hand, so great is the sensitiveness to it, that even half a cup of the moderately strong beverage causes prompt evidence of stimulation, or even intoxication. I know an elderly woman who has for years been unable to take a full cup of coffee at one time, without a feeling of dizziness, and some difficulty in walking straight.

There is perhaps no evidence that the use of coffee directly leads to degeneration of any organ, although in excess it may well be suspected to produce such effects, but it must be classed with those agents that are called, not improperly, poisons of the brain. To those not in the habit of using it it is oft-times (in the form of caffeine and its salts) a useful medicine. To such it is a valuable temporary remedy for paroxysmal headaches, and even for the headaches of Bright's disease and those produced by refraction defects of the eyes.

Few substances of daily consumption by mankind produce such diverse effects as coffee. A study of all recorded investigations into

the physiological effects of it would lead to much doubt as to what those effects really are. The more recent researches of Sée, Lapicque, and others, indicate that it is not a heart-stimulant, that it does not enable the system to get more force out of a given amount of food, but that any increased exhibition of force from the supposed stimulating effect of the drug is always at the expense of the reserves of the system. Of one thing the investigators seem to be certain, namely, that coffee lessens sensibility to physical discomfort, and especially to fatigue, and therefore enables one to undergo greater physical strain with a given subjective state, and that it produces a sweet sense of mental comfort and tranquillity, and favors thought.

One cannot long practice medicine in an observing way without discovering that many persons are so susceptible to the influence of this substance upon the nervous system as to be unpleasantly affected by it. When one seeks for the cause of symptoms before prescribing for them, this becomes strikingly apparent. Tobacco is accused of producing dire effects upon the system, and it often does, but it is speaking temperately to say that among the patients who have heretofore applied to me for advice a larger proportion have had symptoms of disease produced by coffee than by tobacco.

Perhaps the most common symptom that is either produced or aggravated by this agent, after biliousness and insomnia, is headache in the form most frequently of migraine, which is increased in frequency and severity in some cases, and in others actually induced. Other frequent symptoms are palpitation of the heart, various neuralgias of the abdomen, heartburn, and water-brash, while those sensations, experiences, and signs usually regarded as belonging to the condition known as biliousness, probably resulting from catarrh of the stomach and hepatic channels, are very common. Some patients experience various erratic symptoms from it, such as vertigo, and other unusual or queer feelings, hard to describe, of the head and of the eyes; others have mental despondency. Numerous patients, too, have cold feet and hands clearly due to this cause, while an occasional one experiences a sense of constriction about the chest, not unlike the girdle sensation of myelitis.

Tea produces symptoms similar to those described, but to a less degree; fewer persons are affected unpleasantly by tea, and the symptoms are less annoying.

As the cause of the symptoms described is a stimulating beverage habitually partaken of, which markedly effects the nerve centres, the diseases and discomforts are necessarily chronic in character. The victims complain of them bitterly, seek advice and prescriptions from their doctors and, as a matter of fact, by the thousands in this country, go on year after year taking enormous quantities of numerous drugs, visiting springs, sanitaria, and "cures," while their symptoms go on, often with very little abatement, sometimes with none, and a complete cure never occurs. Probably one in ten of all adult persons of the community has found that he cannot drink coffee habitually without discomfort or disorder, and has permanently discarded it.

Following are a few cases out of the many that might be cited illustrating and emphasizing the propositions set forth in this paper:

CASE I.—G. H., clerk in a wholesale clothing establishment, aged twenty-one, of healthy parentage, with no hereditary taint or tendencies, has been healthy through life till the present sickness, except that he had typhoid fever four or five years ago, since which time he has not felt as vigorous, and has had backache on severe exertions. About the beginning of the year 1888, without any change in his habits, he began to have daily colicky pains in the upper part of the abdomen. They rarely compelled him to stop work, but often led him to bend his body forward to get relief. They were always aggravated by any delay in his meals, also by long standing, and they were rarely present at night. His appetite was good; bowels slightly constipated. He had, for a number of years, drank two cups of coffee each day, and sometimes a cup of tea. He was advised to stop the use of both, and to take some laxative whenever it was necessary, all of which he did. His colicky pains immediately disappeared, his constipation soon ceased also, and at the end of five months he told me that he had no pain except occasionally on a Sunday afternoon, when he had taken a cup of coffee for dinner, in tentative violation of his rule. He was otherwise vigorous and well, except for a slight cough which seemed to be due to irritation of his trachea and large bronchi, since by physical exploration of his chest nothing pathological could be found.

A peculiarity of this case is the fact that the gentleman had habitually used coffee for several years before the symptoms of pain appeared. There seems to be no explanation of the occurrence of the symptoms at this time, except in a developed susceptibility to the influence of the coffee. This patient was in perfect health four years after the above notes were made.

CASE II.—J. H. M., aged fifty-two, a business man who spends much of his time in his office, but who takes a vacation to his farm several times a year, remaining a few days each time and taking a good deal of out door exercise. He comes of a vigorous family, and has been uniformily healthy and vigorous through life, and at the time the symptoms to be related began, was, as he has been since, apparently in perfect health; he has also been strictly temperate in habits, moderate and exemplary in everything. His complexion has always been florid. He had for probably twenty-five years drank one cup of coffee each morning, and a cup of tea at night, but never used tobacco or alcoholic liquor. In 1888 he complained of a sense of dizziness that seized him occasionally for a moment, particularly when standing and suddenly turning his head to look in a different direction, or when turning a corner in walking. The sensation was momentary, but annoyed him much, since it suggested to him the possibility of apoplexy. I prescribed for him laxatives and bromides with ergot, but he did not improve. The prescriptions were varied from time to time, gastric tonics were given, sometimes with the addition of iodide of potassium. He failing to improve under any of my prescriptions, I suggested that he stop all medicine and omit his one daily cup of coffee. He told me that he knew the coffee could have nothing to do with his symptoms, for he had used it since boyhood, but that he would omit it to please me. It was more than a year afterward that I next met him to inquire what had become of his dizziness. He assured me that he had faithfully carried out my suggestion, and that the dizziness had completely disappeared on stopping the coffee, and had not returned. He had taken no other treatment, and had not otherwise changed his occupation, regimen, or mode of life.

CASE III.—H., aged forty-six, a travelling salesman, a stout, vigorous, and healthy man, temperate in habits and energetic; uses little or no tobacco. He asked me the explanation of his inability to drink coffee, which, as he was very fond of the beverage, was a great annoyance to him. He said that earlier in life he had been able to drink it with impunity, but that there had developed within a few years an idiosyncrasy of the most striking character. Within a half hour after taking a cup of coffee a severe pain would develop in the epigastrium of a colicky or more or less continuous character, but so severe as to compel him to lie down, press his hands into his abdomen, and bend his body forward. This suffering would continue for an hour or more. He had at intervals of weeks and months ventured to repeat the experiment in the hope that his weakness had disappeared. While in Milwaukee, shortly before his visit to me, he had taken a cup of coffee with a friend at dinner, and, half an hour afterward, while out walking with his friend, the pain seized him with such violence that he was obliged to return to his hotel and go to bed and remain during the whole of the afternoon. Evidently the idiosyncrasy was not growing less.

CASE IV.—Mrs. X., aged forty, a healthy-looking, spare woman, had had since her eighteenth year, till within three or four years, an occasional par-

oxysm of severe pain in the epigastrium, radiating at times to a slight degree in various directions, and lasting a number of hours. There was little or no tenderness either during the paroxysms or between them; rarely did vomiting occur, and no particular symptoms of the bowels had marked the attacks, although she had had intestinal catarrh, at times, for a number of years. She located the pain in the stomach. The most careful observation had failed to convict any particular article of food as the cause of the attacks, although certain articles had, naturally, been found to be less digestible than others. Her diet was altogether wholesome, but she drank two or three cups of coffee each day. Latterly the attacks had become much more frequent than formerly, so frequent, indeed, that life had become more of a burden than a pleasure.

In consultation with her physician, I attempted to discover (as he had before) by interrogation of her organs, some local disease that could account for the symptoms, but found none. As the cause of the attacks was in doubt, she was asked, by way of eliminating a posible etiological factor, to omit her coffee for a few weeks and observe the effect, and to refrain from the use of any drugs that could possibly influence the pain. This she did with the result of stopping the disorder promptly. She reported, after some thirteen weeks, that she had had no pain, save on two occasions to a trifling degree, and she was able to account for one of these experiences by some coffee ice-cream, and for the other by some coffee-cake which she had inadvertently eaten. She now told me that she remembered that the paroxysms of pain began simultaneously with the habit of coffee-drinking over twenty years previously.

The following case is reported for its bearing on the general subject, although tea instead of coffee was used:

CASE V.—Miss G., aged twenty-seven, employed as some sort of a clerk, had been through life healthy, and had all the appearance of vigor. She complained of varying pains in the precordial region, a sense of pressure over the whole anterior portion of the chest, palpitation and irregular heart action, slight discomfort in the head, and a sense of fear, of apprehension of some impending danger. She was nervous about herself, and very apprehensive, and in this particular strongly resembled certain mild cases of delirium tremens.

It was impossible to demonstrate organic disease of any structure of her body, and her physiological functions, except in the particulars of the symptoms referred to, were performed fairly well. She confessed to chewing green tea almost constantly; she had a quid between her teeth and cheek a large part of the time. There was no other discoverable cause of the symptoms, and this seemed sufficient. She told me also that on the importunity of her mother, she had promised and tried to stop the habit, but had, in spite of her resolution, gone back to it again, and she wished my aid to break off effectually before her mother discovered her relapse. With the assistance of

a tonic and some moral support, she succeeded in a few days in stopping her tea entirely, and in as many weeks she was free from all its symptoms.

This is a more striking case, in the degree of chest oppression and mental apprehension, than any that has come under my observation produced by coffee, but it does not differ from some of the coffee cases in any other particular.

A susceptibility to the injurious effects of coffee evidently depends upon conditions of the system that are not entirely constant, but change with the changing of the environment, of the character of the life and labor, and particularly of the age of the individual. A person may pass into the susceptibility after years of freedom from it; as he may pass out of it after experiencing it for years. Case II. is a fine example of the former, and Case I. illustrates the same principle only in a less degree; while the latter is well shown by the following case:

CASE VI.—Mrs. B., aged seventy-four, has been all her life a dyspeptic, and, during her earlier years, subject to frequent attacks of the most distressing form of migraine, often accompanied by vomiting. For more than forty years she probably averaged at least twenty such experiences annually. She early learned that coffee, even taken in moderation, produced symptoms of biliousness, belching, sour eructations, and gastric discomfort, and that these symptoms invariably invited the attacks of headache. Consequently she refrained generally from the use of coffee, although she regularly took tea; but she would occasionally experiment by taking a cup of the more fragrant beverage as a sort of test, instinctively made, of whether it had ceased to be harmful to her. As the years crept on she found her susceptibility was growing less, but it was not till after her sixtieth year that she found she could drink a cup or two of coffee each day with complete impunity.

The following case well illustrates how symptoms clearly not first produced by coffee, may sometimes be lost on omitting it:

CASE VII.—Mr. B., aged forty-five, son of a mother similarly afflicted, had migrainous attacks from his tenth year, at first infrequent, but after his fifteenth year as often as once a month. Numerous forms of medication were tried for it, but with only trifling benefit. He was otherwise in good health. About his thirtieth year the attacks became more frequent, albeit some of them were less severe than those of former years, and were a serious hindrance to his pursuits. The trouble grew worse till his thirty-fifth year, when he suddenly, on the advice of a physician, stopped the use of his coffee —two cups each day—with the result of an immediate almost complete

emancipation from the headaches, and the immunity has since increased in degree.

The curious fact in this case is that the patient never drank coffee habitually until he was twenty years old.

Why the susceptibility to coffee changes in this manner is, of course, as much unknown as is the basis of any idiosyncrasy; but it offers a strong suggestion, if not some proof, that the human system, to numerous other drugs and perhaps foods, has a like changeable and changing response.

A considerable proportion of people may, as far as is known, use tea, coffee, and tobacco habitually without appreciable harm; at least the omission of these agents for weeks at a time fails to produce any different conditions or symptoms in the body. For such no suggestions are needed; and those who have symptoms of sickness when they take such agents, and escape them when they refrain, have the option of taking the luxuries and discomforts together, or living simpler lives with less suffering. The greater pity is that so many should go on year after year, enduring a perfectly preventable sort and measure of suffering, in unconsciousness of its cause and remedy, to whom the luxury of any mere beverage is the veriest trifle.

The experience of susceptible persons in stopping suddenly after having used coffee regularly for years, is often painful as well as interesting. Headache often occurs during the first day or two in so severe a degree as to compel the individual to keep his bed, a result of the sudden cessation of an accustomed stimulant on which the nervous system has learned to depend for support or comfort. Nor is this experience confined to those who have repeated headaches while using the coffee; it occurs to some who are singularly free from this symptom. It may be prevented by reducing the rations of coffee gradually through a week or more of time.

The relief of the coffee symptoms on refraining from the beverage is usually prompt, especially as to the symptoms of biliousness, water-brash, and insomnia, but all the good effects are not experienced for six to eight weeks, that time being required for the system to recover from all the abnormal symptom habits acquired during the use of the drug. A coated tongue due to coffee biliousness may be several weeks in clearing off completely after the coffee is cut off.

Occasionally constipation to an annoying degree follows for a time

the stopping of the coffee, but this can nearly always be corrected by daily laxatives, which later can be reduced and finally omitted altogether.

The following *conclusions* on the subject under consideration seem justifiable:

1. Numerous gastric, nervous, and cardiac symptoms are produced in a proportion of persons by the habitual use of coffee. Among these symptoms are biliousness, insomnia, heartburn, water-brash, acid dyspepsia, palpitation of the heart, cephalalgia, migraine, dizziness.

2. Such symptoms, so caused, may be palliated or stopped for a time by treatment, but cannot be cured while the beverage is used.

3. Whenever these symptoms exist, and are not manifestly due to other causes, and especially when, in the absence of a determined etiology, they fail to yield readily to treatment, the coffee should be rigidly refrained from for at least two months. If during that time the symptoms disappear, it will be proof of both the cause and the remedy.

ON THE PARASITIC NATURE OF CANCER.

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In making an investigation into this subject it is necessary to take for comparison a condition where undoubted parasites produce changes in an organ or tissue which are equivalent to a new growth. For this purpose psorospermosis in the liver of the rabbit is generally admitted to be a typical condition, and a careful study of the changes found there and the relation of the parasite to the newly formed tissue should be fully determined in the first place, so that the process can be followed out in the cells of a growing carcinoma, where, from the arrangement of the tissues, this is infinitely more difficult.

On cutting into one of the small nodules found in the rabbit's liver a substance can be expressed having a yellowish tint. This is found under the microscope to consist of large oval bodies with others of smaller size varying in form, epithelium shed from the bile ducts, and leucocytes. On making sections through one of these nodules it is found to be composed of dilated bile ducts, the spaces in which are filled by masses of the material just described. The large oval bodies are seen, some free in the cavities, others wedged in between the epithelial cells lining them; the smaller rounded forms occupy the same positions. It is evident that having proceeded so far, it is necessary to find some means by which these parasites in their various forms can be differentiated with absolute certainty from the cells of the bile ducts, or their relation to one another cannot possibly be determined. This can only be done by double staining in such a manner that the parasites are colored distinctly from the cells of the part and their nuclei, and this staining must be uniform throughout the section and not in patches, and every section must stain alike.

After trying a large number of coloring agents, I have succeeded

in producing a double stain which will fulfil these conditions. It is made as follows: Dissolve 2 c.c. of anilin oil in 10 c.c. of cologne or rectified spirit, and make up to 100 c.c. with distilled water, and filter. This makes practically a saturated solution. With this anilin water make a 2 per cent. solution of rosanilin sulphate for stain No. 1, and a 1 per cent. solution of iodine (not methyl) green for solution No. 2.

To use the stain, filter No. 1 into a watch-glass and place in it some sections of rabbit's liver which have been hardened in alcohol, and leave them in for ten minutes. Remove and wash them in water to remove superfluous stain, then wash slightly in ordinary alcohol and place them in a watch-glass of filtered No. 2. It is better not to time them in the second stain, but to take them out and examine in distilled water, and when the original red color has become changed to a dull purple the staining will have proceeded far enough. Then wash thoroughly in distilled water until all excess of color has been removed, then wash in ordinary alcohol until no more color comes away, clear in oil of cloves and mount in xylol balsam. On examining a section prepared by the above method it will be seen at once that there is no difficulty in differentiating the parasites from the tissues affected by them.

APPEARANCES PRESENTED BY THE PARASITES.

1. Large oval cells, each with a capsule stained slightly a dull red, having inside a mass of material which has been stained a brilliant red.

2. Shrunken, wrinkled capsules, some empty, some with a small mass of granular material in them, which, however, has not taken the bright red stain. A few of these empty capsules show a number of sharply defined black granules.

3. Large oval cells without a capsule, having a granular appearance, the whole stained slightly a dull reddish color. In addition to these are cells of the same character, but round in outline. These are probably the large oval cells in transverse section. These cells vary, some show a coarse granulation amounting to a network, while in others the granulation is very minute. Some also show a small, round nucleus. Their size also varies, but the smallest is many times larger than any single columnar cell lining the bile ducts.

APPEARANCES PRESENTED BY THE ALTERED TISSUES.

A section through the dilated bile ducts shows a number of spaces or cysts lined with columnar epithelium, and into these spaces project papillomatous folds which branch and are also covered by columnar epithelium. These folds consist of fibrous trabeculæ varying in thickness, having a homogeneous basement membrane on which the epithelium is situated. In the more delicate trabeculæ, that is those most recently formed, the connective tissue is in process of development and contains a large number of young connective tissue corpuscles. At the base of these folds this young connective tissue can be seen penetrating the liver substance and isolating the liver cells, so that in the substance of some of the folds one or more rows of liver cells are still left surrounded by connective tissue.

ACTION OF THE STAINS ON THE TISSUES.

The green stain has picked out all the nuclei by its action on the nuclear network with the exception of the older connective tissue corpuscles. By this stain the nuclei of the columnar cells covering the trabeculæ in folds are seen to be small, narrow, oval in shape, having a comparatively thick network; the nuclei of the liver cells at the base of the folds are much larger, round or slightly oval, and have a finer network. The nuclei of the young connective tissue corpuscles are of the usual character, and the leucocytes have taken the stain very deeply. These are the only elements stained by the green.

The fibrous tissue and protoplasm of the liver cells are stained a purplish red, and the protoplasm of the columnar cells has taken the same tinge, the color being darker in the liver cells than in the other two.

THE RELATION OF THE PARASITES TO THE ALTERED TISSUE.

Taking a section which has been cut as thinly as possible, and in which the different elements have been differentiated as described above, we find in the first place a mass of parasites filling up the spaces between the folds, a number of them being a bright red, the others having only a faint tinge of dull red; amongst these are a

number of desquamated columnar cells in various stages of disintegration, their nuclear network, however, is stained brightly with the green. There are also a number of deeply stained, small, round cells (green) which appear to be leucocytes. On examining the epithelium we find wedged in between the cells a number of the parasites, some in the capsulated form a brilliant red, others a dull red with no capsule. They are plainly wedged in between the cells and reach down to the basement membrane. It is, however, a difficult matter to get at the exact relationship of one to the other in the section of the fully formed fold. But if we look for a small bile duct in which the process of dilatation is only just commencing, it becomes an easy matter to understand it.

There are a number of small bile ducts to be found at the base of the folds, which contain several parasites, and in proportion to the number of these has the process of dilatation advanced. In the smallest a few parasites are seen, one or two adult forms, while there may be five or six that have not developed a capsule, the majority, however, are free in the lumen of the duct, a few are wedged in between the cells. In some ducts the process has gone further, and small folds are just beginning to form, and in these ducts the lumen is much larger and the parasites more numerous. The relation of the parasites is, however, very plain, and by using a binocular microscope with a high power it can be ascertained beyond a doubt; the parasites that are wedged in between the columnar cells by their growth and presence cause desquamation and disintegration of contiguous cells, but in no case are they contained in the columnar cells. This would be a physical impossibility, as the smallest forms of the parasites are much larger than the columnar cells. It is, of course, possible for the parasite in an early stage of its growth to get inside a cell and expand it as it grows. I cannot, however, find any parasite small enough to do this, neither do any of the columnar cells show evidence of any displacement of their nuclei, which must take place if another body was growing inside them.

On examining some of the large cells that have no capsule, a few will be found which have had a portion cut off in making the section. These cells show a margin of granules, while the centre is free from them. This shows that the granules are on the outer margin of the cells, and the binocular microscope confirms this view. We have, then,

a large oval cell having a granular covering. On examining a number of these it is at once apparent that this granular covering varies very much in different cells. In some it is very fine and difficult to make out, having scarcely any appreciable thickness; in others the granules are much larger and the coating is thicker. Further examination shows that this granular covering increases in thickness and in the size of its elements until definite patches are seen covering the cell. In some this change has gone on until the cell is almost covered; this is the development of the capsule, and the appearances described might easily be considered as the expansion of one cell by the growth of another inside it. All these stages in the development of the capsule can be seen going on in the spaces of the dilated bile ducts.

It seems to me that this explains the view held by some that the parasite inhabits the cells of the bile ducts. If we consider the enormous number of parasites that are found free in the spaces of the dilated bile ducts and the very small number that are found wedged in between the cells, also that every stage in development is going on in those lying free, and also take into consideration the fact that the smallest form of the parasite that we can detect is very much larger than the columnar cell of the bile duct, it seems to me that we must accept as a fact that the action of the parasites is simply one of chronic irritation caused by their rapid multiplication in the lumen of these vessels. This is a very important consideration, as we do not know how far in many cases new growths are produced simply by chronic irritation. I have seen several cases where horny growths which had existed for many years were converted into epitheliomata by the action of irritants. In another case, where lycopodium had been used as a dressing, I found the seeds deeply imbedded in a new growth. They may, of course, have had nothing to do with the formation of the neoplasm. But in a case of villous growth in the bladder removed by Sir Henry Thompson, I found a wheat straw imbedded in its centre. In this case I have no doubt the new growth was caused by the foreign body.

The next question to be considered is the cancer parasite and its relation to the cancer cell. On reading the recent literature on this subject, the first thing that strikes one is the diversity of opinion that exists as to the appearances presented by the parasite and its frequency, some observers finding it in every case in such numbers that

it could be estimated by weight, while others found it in only about 4 per cent. of the cases examined. From the illustrations given it would seem that all the observers were not looking at the same object. Some give special methods of hardening the tissue, while others found the parasite in material hardened in the usual manner.

To test the value of these special methods and find out what their action would be on tissues, I hardened portions of a fresh cancer by the methods used in my laboratory, and also by bichloride of mercury, osmic acid, and Muller's fluid and some other methods described by different observers, at the same time I hardened portions of normal ox liver by all these processes. Sections were made of all the material, and stained with logwood, and also with the special stain I have already described. The sections of cancer and liver hardened in the usual manner showed the normal liver as it is known to be, while there was nothing to be seen in the sections of cancer which could be considered parasitic; but in the sections hardened in bichloride of mercury and in osmic acid and Muller's fluid, both liver and cancer were so much altered by the hardening process that it was not difficult to realize how the characteristic organism of cancer could be found and estimated by weight. Those observers, however, who have only found the so-called parasite in a small percentage of the cases examined have not been describing effects produced by bad hardening. The appearances they have figured I have long been familiar with; they are, I think, capable of a different explanation from that given. I have gone over the large collection of cancer specimens I have made in the last fourteen years, and I find these appearances in only a few of them. In 1879, while working at karyokinesis, I obtained a specimen of cancer in the fresh condition, which after hardening showed in the section a number of very large cells. In these I found mitotic division most beautifully shown, but the process was going on inside the large cell; the original cell was enormously enlarged, its nucleus and some of its protoplasm pushed to one side, while in the centre was a small mass of protoplasm containing a nucleus. This nucleus in various cells showed all the stages of mitotic division from the simple aster to two fully formed nuclei. I considered this to be a typical example of the endogenous division of cells. In 1886 I photographed this specimen amongst a number of others, showing various conditions in cancer development, and in 1891 I used this as an illus-

tration of endogenous division in my work on *Practical Pathology and Morbid Histology*. I have only a few cases in which this process appears.

For the purpose of studying the parasitic nature of cancer I have used cases where the development of the cells can be observed, such as in the axillary glands, where the process is secondary to carcinoma mammæ, and where the operation was performed in an early stage of the disease, and also in cases where recurrence had taken place and the growth had been removed twice or three times. In recurrent cancer of the breast small nodules are found in the muscles, and their development and relation to the muscular tissue is very interesting. Examining that portion of a section which shows the cancer cells invading the muscles, changes in the muscular fibres which are at some little distance from the cancer cells are at once apparent. Some of the fibres show spaces in their substance somewhat similar to the appearances found in striped muscle in cases of myxœdema, in others the muscle substance is completely broken up and the muscle corpuscle is seen as a shrunken nucleus surrounded by an empty space. All these changes take place before a single cancer cell is in apposition with the muscle fibre.

The next change is the appearance of one or two cancer cells in the centre of the broken down muscle fibre. These increase until the fibre is replaced by cancer cells and the sarcolemma is either changed into fibrous tissue or is replaced by it. The method by which the cancer cells gain access to the centre of the muscle fibre is not apparent, and requires further investigation. In all these cases active growth of the cancer elements can be accurately observed; and as I hold that where a pathological process is in an active stage of development there the cause, if capable of demonstration, should be found. I consider that in these cases I ought to find the parasite, if the disease process were caused by one. The most careful examination of a number of cases has failed to show anything that could be construed into any form of parasite, that is, in those sections hardened by a method which gave normal appearances in sections of normal liver.

When we consider the many different forms of cancer, it does not seem possible that they can be the result of the action of any one form of parasite, and further, when we study the differences between two forms such as squamous epithelioma and glandular carcinoma, we

find the differences so marked, that, although they have certain points in common, yet they are practically different diseases. In squamous epithelioma we have a condition in which the epithelium receives some impetus at a certain point which causes it to grow downwards into the tissue below, and there to branch out in every direction. It is at the one point, however, that the growth takes place, and the newly formed epithelial tissue will grow sideways under the normal epidermis without having any effect on it. It has also no effect on the fibrous connective tissue into which it grows as a rule. I have, however, seen an enormous hyperplasia of yellow elastic tissue produced by the growth of an epithelioma in the eyelid.

On the other hand, we have a glandular carcinoma starting in secretory epithelium and consisting of cells derived from this epithelium, and in every case this new growth affects the fibrous connective tissue in such a manner that a supporting framework is formed for it as it grows, and in this are contained new bloodvessels for its nourishment. Although these two forms differ so much in their construction, there is one point of absolute resemblance between them. A cell from either form on being carried to a distant organ will at once reproduce a cancer of the same type as that from which it started. It therefore follows that if a parasite is required, it must be the cell itself, but that gives no explanation as to how the first cancer cell became cancerous.

Sarcoma must be considered on an entirely different basis. Where I have been enabled to examine a sarcoma in its earliest condition, that is, where a young growth is starting in connection with an established sarcomatous condition, I have found that it always consisted of embryonic connective tissue, and according to my observations all mesoblastic neoplasms begin in this way. Whether they receive the impetus which decides that they are to become sarcomata, or remain benign at the commencement or later in their growth, would seem to vary in different cases.

CONCLUSIONS.

1. The dilatation of the bile ducts in the liver of the rabbit is caused by the chronic irritation produced by the multiplication of the coccidium oviforme (Leuckhart) in them, and the appearances which have given rise to the view that these parasites are developed in the

columnar cells of the bile ducts, are caused by the different stages in the development of the capsule.

2. The appearances found in a small percentage of glandular carcinomata are caused by endogenous cell formation, the large majority of glandular carcinoma show nothing which can be considered parasitic when hardened by any method which, when applied to normal tissue, will give a typical normal section.

THE IMPORTANCE OF UTERINE DISPLACEMENTS IN THE PRODUCTION OF VOMITING DURING THE EARLY STAGES OF PREGNANCY.

By GEORGE M. GARLAND, M.D.,
OF BOSTON.

In a former paper read before this Association I discussed the subject of so-called cyclical vomiting. A study of that class of cases shows that the nerve-centres which govern the functions of the stomach may be in some persons so prone to excitability that very inefficient causes will produce excessive and even dangerous attacks of vomiting. A study of vomiting during pregnancy will also reveal similar cases where no sufficient provocation can be discovered. On the other hand, there are many cases wherein a cause for vomiting may be readily found and remedied. Dr. Graily Hewitt divides the vomiting of pregnancy into two groups: vomiting which is produced by causes remote from the womb, as by acute congestion of the kidneys, for instance; and vomiting which is due to some mechanical trouble in the womb itself. In this paper I desire to call attention, very briefly, to the great importance of the last-named class of cases, that is, to the vomiting which is caused by some malposition of the womb.

A few years ago, in the early days of my practice, my friend, Dr. W. E. Boardman, of Boston, once remarked to me that he thought the majority of the discomforts of womb displacements were due to the one element of *prolapse*. Provided the womb be maintained at a proper height, flexions and versions are of no consequence.

My own experience corroborates the accuracy of this observation of Dr. Boardman, and it has led me to study the position of the womb during pregnancy with reference to the discomforts of that period. My obstetrical practice is not large, and, therefore, it is not safe for

me to generalize too widely upon the limited number of cases which I have seen; but I have observed several cases where prolapse alone seemed to be the cause of the vomiting, the womb being otherwise in normal attitude. In such cases I place my patient in the knee-shoulder position, and by opening the vagina allow the womb to drop into place, and oftentimes this manœuvre will stop the vomiting without further interference.

But when the womb is prolapsed and begins to grow with pregnancy, and when at the same time the body is verted or flexed so that the fundus lies behind the symphysis or back in the hollow of the sacrum, the organ very soon becomes impacted, and then follows those direful attacks of vomiting which are so distressing to the patient and friends. Such cases are very lucky ones for the physician, however, provided he discovers the real state of affairs, because there are no troubles in the whole gamut of disease which are more amenable to treatment. Put the womb back in place and keep it there, and the vomiting will cease.

I desire to specify a few cases which I have observed during the last few years.

CASE I.—Mrs. H., primipara, twenty-two years of age, about two months along. I was called to see her on Sunday, July 3, 1892. She had been vomiting incessantly since the previous Tuesday. Food and drink were instantly rejected by the stomach. She was excessively emaciated, and there was a large ecchymosis over the crest of the ilium on the right side, which had appeared that day and without known cause.

The womb was as large and broad as it should be at that stage of pregnancy. The fundus was quite firmly wedged behind the symphysis; the cervix was soft and flexed in its upper third. The womb was not very tender to pressure. I replaced in the knee-shoulder position with some difficulty, owing to the wedging of fundus behind the symphysis.

No medicine was given. The patient did not vomit for more than twenty-four hours, and her appetite began to come back. On the afternoon of July 4th she vomited once, and I found the womb again wedged. I replaced it and held it by a tampon. In the early morning of July 5th she vomited once more. I took out the tampon and inserted a soft rubber ring. The patient was so much improved that she craved meat and a general diet; in fact, she ate so heartily that she brought on a typical sick headache, which lasted a few hours, and was relieved by a purgative. After this there was no more nausea or vomiting during the remainder of the pregnancy.

CASE II.—Mrs. B., second pregnancy, about four months along, complained of occasional attacks of severe pain in the abdomen, accompanied by

vomiting. The womb was tipped forward and wedged. It was replaced without pessary, and there was no further trouble during the pregnancy.

CASE III.—Mrs. M., between two and three months along, complained of nausea, vomiting, and discomfort on walking. The womb was simply prolapsed. Replaced, with relief of symptoms.

CASE IV.—Mrs. D., pluripara, about two months along, had suffered three weeks of severe vomiting, was confined to bed, and had tried many drugs without avail. She had taken a morphine suppository of one-fourth grain strength, with very little effect, on the evening before my visit.

The womb was anteflexed and sinistro-verted. It was not impacted, being freely movable. The womb was replaced. During that day she was given one more morphine suppository by her mother. The vomiting ceased for forty-eight hours, and then returned as bad as ever. The womb was again replaced and held by a pessary. The relief was marked and the patient gradually recovered. The case, however, was complicated by a large amount of albuminuria. In spite of the kidney complication, the simple replacement of the womb did rapidly what many drugs had failed of doing.

CASE V.—Mrs. M., pluripara, about two months along, very nervous woman, suffered from puerperal mania with first child, came to my office complaining of an incessant disposition to sigh. Her conversation was constantly interrupted by a deep, prolonged sighing, which was exhausting her strength.

I found her womb retroverted to the third degree. I replaced it and supported it by a pessary. The sighing was immediately relieved. After about two weeks the patient removed the support, and the sighing returned. I found the womb again retroverted as before; I replaced the womb and pessary, and there was no more sighing during the balance of the pregnancy.

CASE VI.—Mrs. W., primipara, twenty-three years old, unwell last September 27, 1892. All right until November 8th, when she experienced nausea part of the day. The nausea came, off and on, until November 12th, when she vomited five times. Vomited still oftener on the following day. At first the nausea was better when she lay down, but now she has it all the time. I saw her first on November 16th, *i. e.*, at the end of her sixth week.

I found a small horseshoe-shaped womb, prolapsed on to the perineum and completely dextro-verted. (She had always "suffered dreadfully" during her menses.) There was no tenderness anywhere and no impaction. The womb was replaced and supported by a pessary. There was no albumin in the urine. During the following week the patient was very much improved: her appetite came back; she had a little nausea and vomiting in the morning on first rising, but felt well the balance of the day. She then went away on a visit to her mother for Thanksgiving. When she returned she said she was all right, and has had no trouble since.

CASE VII.—Mrs. C., primipara, twenty-two years old, six weeks along, had been complaining of slight nausea for a few mornings, was then taken very dizzy while driving. On returning home she could not move about without dizziness and nausea, so that she was compelled to go to bed.

I found the womb anteflexed and completely dextro-verted. It was not tender or impacted. I could easily replace it as she lay on her back. She was better all day, but the next morning was nauseated and was trying hard not to vomit at the time of my visit. I found the womb in the same malposition as on the previous day. I again replaced it and the nausea disappeared. The womb stayed in place this time, and the patient had no more vomiting or nausea.

I will say that in all my cases I insist upon the abandonment of the corset and the substitution of a loose waist adapted to support the skirts from the shoulders.

From my study of the above cases, I had concluded that *prolapse* of the womb, either simple or complicated, with a version to one side or the other, or backward, was the more frequent cause of the nausea and vomiting in pregnancy, and my conclusions were strengthened by the fact that simply tumbling the womb back into place in the knee-chest position gave immediate relief in them all.

The terrible vomiting, pain, etc., occurred only when impaction was present, except in one case, where albuminuria was also found.

On reading Dr. Hewitt's book, which I saw for the first time only a few weeks ago, I find that he lays most stress upon anteflexion as the cause of the vomiting. He says:

"It has been shown that impaction of the uterus in an anteflexed state is observed in a considerable number of cases of severe vomiting of pregnancy. The occurrence of impaction under such circumstances requires to be attentively considered, as it is evidently an important factor in the causation of the vomiting."

Later on he adds:

"When the impaction persists it causes intense degrees of vomiting. Whatever view may be taken of the cause of the impaction, it appears that it can, in the worse cases, be relieved by mechanical means. The impaction is relieved, and its effects (on the vomiting) removed by artificially elevating the fundus; and this is a procedure which, necessarily, more or less alters the shape of the uterus and lessens the degree of the anteflexion present."

While thus accrediting much blame to the impaction, he, nevertheless, believes that the flexion of the womb is the chief factor, and even with impaction, he says the latter difficulty is relieved by *raising the fundus*, and thus lessening the flexion. I cannot agree with Dr. Hewitt in this explanation, because he states only half the facts.

Not only the fundus is raised when the impaction is relieved, but the *entire womb* is elevated with all its circulatory apparatus, and the *flexion still remains.*

Dr. Hewitt claims that in pushing up on the fundus one must necessarily straighten out the flexion somewhat; but in several of my cases where the womb was anteflexed, prolapsed, and twisted latterally, I did not have to push—the organ tumbled into place of its own accord when the patient took the knee-chest position and the vagina was opened. The anteflexion still remained, and yet the nausea and other discomforts were banished.

In a case (Case VII.) which I examined yesterday with reference to this very point, I could detect no difference in the degree of *anteflexion* after replacement, but the whole womb, which previously lay on the floor of the pelvis, was well up in the median line, and the dizziness and nausea were relieved.

I cannot deny that an anteflexion may be so severe and the rigidity of tissues at the flexion be so great as to cause vomiting, but I do maintain that with the flexion still persisting and not appreciably altered, but with prolapse and impaction corrected, the vomiting does cease.

Dr. R. A. Kingman, in an interesting article upon this same topic (*Boston Medical and Surgical Journal*, November 3, 1892), speaks of two cases of pregnancy complicated with retroverted uteri which had no vomiting at all. One complained of severe headache, and aborted at three months. In the second case he gradually worked the womb into place.

Such cases are interesting from a physiological standpoint, by demonstrating how much strain some nervous systems can stand without yielding, where others give way on the slightest provocation.

In conclusion, let me say that this paper is not a discussion of the subject of pregnancy-vomiting in its whole extent, but it has been arbitrarily and explicitly restricted to one phase of that subject, viz.: to the discernment and treatment of such cases of pregnancy-vomiting as are due to a malposition of the womb.

In thus restricting the scope of this paper, however, I believe that I cover a large percentage, more than a mere majority, of the cases of nausea and vomiting during that period. I formulate my belief in the following propositions:

1. Prolapse of the womb, whether simple or complicated by retroversion or anteversion, is a more common cause of vomiting in pregnancy than is generally supposed.

2. The severity of the vomiting is usually excessive in proportion to the degree of incarceration of the womb consequent upon the prolapse and the pregnant enlargement of the organ.

3. Such vomiting is usually controlled by replacement of the womb, *i. e.*, by elevation of the organ out of the pelvis and by a support to keep it elevated.

TWO CASES OF DIAPHRAGMATIC HERNIA.

By JAMES TYSON, M.D.,
OF PHILADELPHIA.

Case I.—C. B., aged twenty-five years, was a hearty, vigorous man, when, in the month of February, 1880, while stretching, his wife suddenly "tickled" him under the arm. He threw his arms down quickly, and at once felt a sensation as though something had given way on the left side in the vicinity of the heart. He became faint and cold. In five or ten minutes these sensations passed away, although he remained very much frightened.

When he visited me June 21st, his appearance was that of a vigorous man, but he complained of shortness of breath and "beating" of the heart—both symptoms abating somewhat when he was quiet; in fact, he could not even walk across the floor without becoming completely out of breath; much less could he do any work.

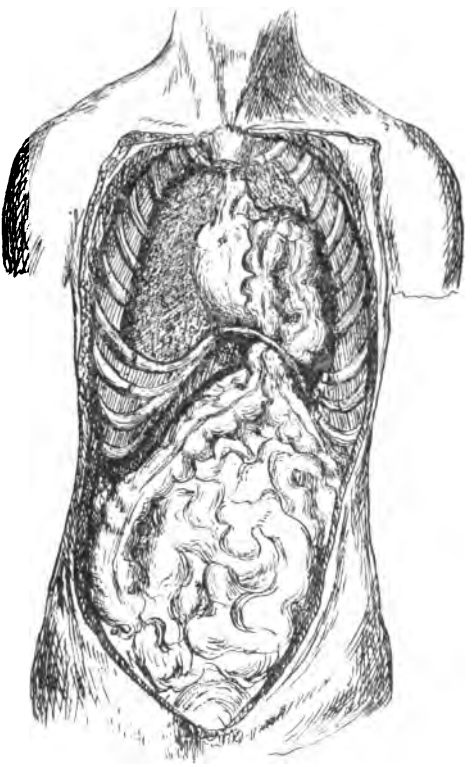
Physical examination revealed to inspection almost total absence of motion in the upper thoracic walls, the breathing being nearly purely abdominal. Vocal fremitus was diminished over the whole of the left half of the thorax, while the percussion note seemed slightly less than normally resonant below the angle of the left scapula; otherwise the note was normal. His pulse was but 72 after the examination was completed.

Under the influence of full doses of digitalis he improved somewhat, but the improvement was but temporary, and he continued to be breathless on the slightest exertion, and was subject to spells of faintness, which were very annoying. At times he would complain of a sense of constriction about his heart, and a sensation as though his heart was fastened. He said also that he slept better on his left side, but that his sleep was generally limited to periods of two hours, because of his heart, which would arouse him at the end of this time. Later he could only sleep on his back, but he always lay more comfortably on his left side than on his right, the sense of cardiac constriction increasing as he turned toward the right. He also made the very expressive remark that he breathed more on his right side than on his left. He always felt worse after eating.

All of these phenomena were amply explained in the light of the autopsy, but he continued to be an enigma to me. I sent him to Dr. Pepper for an examination, but he reported negatively, and was inclined to believe with me that there was a large neurotic factor in the case, and that the man was

not as ill as he thought. The patient's pulse and respirations grew gradually more frequent. At the first visit, as stated, the pulse was 72; the respirations were not noted; but at his second visit, two weeks later, July 8th, the pulse was 96 and the breathing 42; October 13th, pulse was 84, respirations 30; November 4th, pulse 96, respirations 40; December 28th, pulse 108; January 3, 1881, pulse 96; January 19th, 96. At his last visit to me, May 27, 1881, it was 108.

After the last date I did not see him again. He died a year or two later, and an autopsy was obtained and made by the late Dr. Formad. Unfortunately, the records of the autopsy were lost, but the accompanying drawing,



Diaphragmatic hernia.

made at the time, is more expressive than any words can be. It will be seen that a very considerable portion of the small and large intestine has passed through the œsophageal opening and ascended into the thorax, encroaching upon and displacing the heart, and causing the embarrassment of which the poor fellow complained so bitterly, but which we were inclined to believe was largely imaginary.

CASE II.—C. J., colored, aged thirty-nine years, was admitted to the Hospital of the University of Pennsylvania, September 12, 1891. The patient said he had been vigorous and healthy until three years previous to admission, when he was struck by a car, with the effect of breaking, he said, five ribs, the sternum, and scapula, for which he was treated in the University Hospital. He appears to have recovered from the effect of this injury, and claims he was perfectly well until the day before admission, when he went on a spree, drinking a pint of whiskey and a large amount of beer in a very short time. His last drink was followed in an hour by vomiting, which lasted all night and was accompanied by abdominal pain. The next day he attempted to go to work, but was unable to get to it on account of pain, and was brought to the hospital in the police patrol wagon. On admission his pulse was 88, respirations 21, and temperature 99°. His abdomen was retracted, and he complained greatly of abdominal pain, especially in the neighborhood of the umbilicus, which was eased by drawing up his legs, and especially by getting upon his knees with his head upon a pillow, relaxing thus his abdominal walls. He was constantly found in this position when the ward was visited. The conjunctivæ were slightly icterode and there were a few ecchymotic patches under the left.

A dose of calomel on the day of admission, and later on the same day one of magnesium sulphate, were vomited, as was also a second dose of the salts. On the next day, his bowels being unmoved, a dose of oil, preceded by one-eighth grain cocaine, was, however, retained. In the evening, there being still no movement, an enema was administered and a motion secured. Other treatment was directed to the relief of pain.

I saw him first about noon of the 14th (he was admitted on the morning of the 12th), when he was falling into a collapse, his temperature having been 96.2° at 8 A.M. and 95.2° at 11 o'clock. Physical examination under the circumstances was difficult, but this much was made out: Inspection recognized nothing, but there was evident impairment of resonance over the lower left side posteriorly, associated with diminished vocal resonance and fremitus. On the right side the physical signs noted were essentially normal, but no note seems to have been made of the signs in the upper part of the left side. As there were the signs of a pleuritic effusion in the lower part of the left side, it is presumed that those of the upper were regarded as normal. In view of the subsequent history, it is not unlikely that a careful differential examination would have discovered a hyper-resonance in this situation.

The man died on the evening of the 14th, and an autopsy made, from the record of which the following concerning the thorax and abdomen is taken:

"The left pleural cavity contained about a quart of bloody fluid, together with the greater part of the intestinal canal from the lower end of the duodenum to within eighteen inches of the ileo-cæcal valve. Of the large intestine, the upper part of the ascending colon, the transverse colon, and the descending colon down to within two feet of the anus, were all within the thoracic cavity.

"The orifice through which the abdominal contents entered the thorax was

the enlarged opening of the œsophagus. The large intestine, the mesentery, and a portion of the small intestine in the pleural cavity were decidedly gangrenous, breaking readily and permitting the escape of their contents, which had the appearance of almost pure blood. The left lung was compressed into about one-fifth its natural size. The heart was pushed toward the right.

"The orifice through which the hernia took place shows a pure white edge somewhat thickened, 'evidently not recent.' Moreover, between the portion of intestine in the abdominal cavity and the margin of the opening there were old adhesions.

"The right pleural cavity was almost obliterated by a fine network of old adhesions between the pulmonary and costal pleuræ."

The date of occurrence of the hernia in the first case seems to have been the moment of the sudden motion in the man's effort to escape the playful act of his wife. The date of the event in the second case is not so easily ascertained. The statement in the autopsy, that the *white* edge of the œsophageal orifice was "somewhat thickened, and evidently not recent," is probably the result of a misconception, the anterior margin of this orifice being often white and tendinous in health, formed, as it is, by the margin of the central tendon of the diaphragm. If the protrusion had taken place at the time of the crushing accident one would expect more serious respiratory symptoms to have presented themselves. Yet these may have been present in a very high degree and forgotten by the patient, while violence identical with that at the time experienced by the patient, viz., compression of the lower part of the chest between the cars of a railway train, is put down as one of the causes of rupture of the diaphragm through which such herniæ take place. It will be remembered that there was no rupture in this case, and that the hernia occurred through the œsophageal opening, and it may be that the intrusion took place as the result of the strain in vomiting through an orifice congenitally large or possibly enlarged by the accident. Or a partial hernia may have taken place at the time of the accident, have been in part or altogether spontaneously reduced and renewed as the result of the vomiting. The adhesions noted between the orifice and the viscera on the abdominal side of the opening also point to an earlier occurrence than that immediately preceding admission to the hospital.

Both cases sustained the experience of others, that diaphragmatic hernia is most frequent on the left side, it is said probably owing to

the imperfect support on this side compared to the right, which has the liver directly under it. Very much more extensive herniæ than these are reported, as in a case of Vincent Jackson's,[1] where the stomach, spleen, transverse colon, and part of the small intestine passed through a rent beginning near the middle line in the neighborhood of the vertebral column, and extending thence upward and outward, but not quite reaching the thoracic wall. In another case, reported by Kendall,[2] the stomach, transverse colon, and about two feet of the small intestine had protruded.

The important practical question is the diagnosis of these cases. In view of the extreme rarity of the affection one may be excused for not recognizing the exact state of affairs in the first case, but it would seem that experience in one case might have suggested the correct diagnosis in the second case. Yet the interval between the two cases was so long that, in truth, I had forgotten that I ever had the first case when the second presented itself. Certain it is that a similar combination of symptoms, should it ever occur to me again, would certainly excite suspicion.

It is very likely that a diagnosis being once made, modern surgery would attempt, with reasonable hope of success, to reduce such a hernia through the abdominal cavity.

[1] Medical Times and Gazette, March, 1858, p. 318.

[2] Ibid., 1865, p. 253.

MYXŒDEMA: THE FUNCTIONS OF THE THYROID GLAND, AND THE PRESENT METHOD OF TREATMENT OF MYXŒDEMA.

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THE nature of thyroid tissue, its distribution in the body, its relation to other gland tissue and to the pituitary body, and finally the functions of the thyroid gland, have been the subject of investigation by numerous observers, especially in the last decade.

Victor Horsley, in a critical and historical review of the functions of the thyroid gland, published in 1891, concludes from all accessible evidence that the thyroid gland is a structure essentially connected with the metabolism of the blood and tissues; that in fulfilment of its functions it is hæmapoietic, both directly and indirectly, and that it forms—that is, secretes—from the blood a colloidal substance which is transmitted *via* the lymphatics from the acini of the gland to the circulation.

Evidence that the thyroid gland is directly hæmapoietic rests mainly: 1st, upon the observations of Credé (2) and Zesas (3) to the effect that hypertrophy of the thyroid followed experimental extirpation of the spleen in animals, together with an increase in the number of white cells and a diminution in that of the red corpuscles. Later the leucocytosis disappeared. Horsley also noted clinically, hypertrophy of the spleen following experimental thyroidectomy, a condition verified post-mortem (4); 2d, upon the anæmia associated with cachexia strumipriva. Horsley observed in experimental thyroidectomy in monkeys (5) a continuous diminution in the red blood-corpuscles subsequent to the removal of the gland, with an increase in the leucocytes, but only for a comparatively limited period, when the decrease in the former ceased and an oligæmic

equilibrium was established and maintained until death. He found, moreover (6), definite lymphoid tissue of a distinctly splenic character; also by an enumeration of the leucocytes in the thyroid arteries and veins respectively he was able to show that they were in a greater proportion in the latter, and that this proportion was greater than existed in the vessels of the limbs. In the absence of further evidence on this point, a directly hæmapoietic function of the thyroid gland cannot be considered as yet proven.

The theory of an indirect hæmapoietic function is based chiefly upon the observations of the condition of the blood following thyroidectomy. The changes noted by various observers (Herzen, Hofrichter, Albertoni and Tizzoni, and others) (7) are increased venosity, marked diminution in the oxygen of the arterial blood, even to the degree of its falling below that in the veins, and the presence of mucin in the blood plasma.

Albertoni and Tizzoni were able to demonstrate that the deficient oxygenation was not due to mechanical interference with the respiratory act, by obtaining the same results in dogs, which were tracheotomized after thyroidectomy. Horsley justly remarks that such changes gravely "altering the constitution and functional activity of the blood, must evoke a considerable degree of anæmia, both by destructive changes in the fluid itself and by the effect which it, thus altered, necessarily exerts on the blood-forming tissues, for example, the marrow."(8) Further observations on these points are to be desired.

That the thyroid gland forms or secretes a colloidal substance, which is transmitted *via* the lymphatics from the acini of the gland to the circulation, was apparently first demonstrated by King (9), and later confirmed by Langendorff (10), Kohlrausch (11), Horsley (8), and others.

King's interesting contribution on "The Structure and Adaptations of the Thyroid Gland" was published in 1836, with some additional notes on the same subject by Sir Astley Cooper. The former was able to demonstrate the introduction of the peculiar secretion of the gland into the lymphatics by expelling its contents by gentle and repeated compression into the lymphatics of the surface, and there coagulating the fluid *in situ*. He further considers the sources in the living body of compression and muscular manipulation of the gland, viz., the movements of the larynx, both vertically and toward the spine;

the distention of the œsophagus in the descent of food, and, finally, the action of the muscles investing the gland, the sterno-hyoid, the omo-hyoid, and sterno-thyroid. It is of interest to note that in speaking of extreme fibroid atrophy of the gland, which he had observed in a particular case, he states that "the peculiarities of the individual were fully sufficient to indicate the importance of the defective part."

King, therefore, not only recognized the importance of the functions of the thyroid gland, but possibly had observed the clinical picture which is now known under the name of myxœdema.

Sir Astley Cooper's notes contain a chemical analysis by Babington of the thyroid secretion, from which the latter was led to believe that it was largely an albuminous fluid (9). Passing over other early analyses of this secretion, the chemical investigation of its nature by Langendorff, which is one of the most recent, may be mentioned (10). He examined the colloidal contents of the thyroid follicles with various reagents, and finally, from their behavior with acetic acid, concluded that mucin is not present. The various tests for albumin confirmed the conclusion that the colloid material either consists of albumin, or that it is the chief component.

Concerning the nature of the single or preponderating albumin present, he states that it is not alkali-albumin, unless, as Virchow suggests, it be alkali-albumin modified by a large percentage of sodium chloride. He failed in his analysis to find an appreciable quantity of globulin. The contents of the lymph-spaces were found to be identical with the colloid substance of the follicles. The course of the secretion beyond the lymph-spaces he was unable to demonstrate, and he advances the view that it remains in the gland (in its follicles and lymph-spaces) and becomes dehydrated, and that the unique function of the thyroid gland is to purge the blood of useless or injurious substances.

Whether we accept Horsley's view, that the thyroid gland possesses a twofold function, viz.: "a hæmatogenous and a mucin-excreting one," or we reject the former and believe that the gland "secretes a substance which, entering the circulation, prevents an auto-intoxication by transforming the toxic products of metabolism into easily eliminated bodies, or by directly neutralizing these products," a view at present held by many, the vital importance of a physiological

activity of its functions is to-day recognized by a great majority of observers.

Evidence of the correctness of this view is found:

First. In the developmental history of the thyroid gland.

Horsley has shown that in the human fœtus the epithelial cylinders of the gland begin their secretory functions from the sixth to the eighth month (1). Huschke (12) found that its proportion to the weight of the body in the newborn was that of 1 to 400—243, 1 to 1166 at the end of the third week, 1 to 1800 in the adult. In other words, its functions are well developed in intra-uterine life and early infancy, at a period when metabolism is especially active. Again, in intra-uterine cretinism, which is now well recognized, and in which the cretinic and myxœdematous cachexia is far advanced at birth, as a rule no trace of the thyroid gland is found.

Second. In the ultimately fatal cachexia (cachexia strumipriva), which ultimately follows total extirpation of the thyroid gland in many species of animals. The dependence of the symptoms of cachexia strumapriva upon injuries inflicted in thyroidectomy upon the laryngeal nerves and the cervical sympathetic and vagus, a view first advanced by Munk, has been shown to be incorrect (13). A series of experimental investigations by Ewald, Herzen, Horsley, and others have demonstrated that these nerves can be subjected to every kind of irritation without producing any of the symptoms of this cachexia.

Third. In the similar cachexia, which, in a large number of cases, has been observed to occur after complete thyroidectomy in man.

Fourth. In the clinical events which accompany and follow gradual morbid changes with loss of function in the thyroid gland, constituting a well-defined disease, to which the name of myxœdema has been given by Dr. Ord. The dependence of myxœdema upon such changes has received the most positive demonstration. In the very admirable and elaborate investigation of the subject of myxœdema by a committee of the Clinical Society of London (14), extending over the period from 1883–1888, in thirteen autopsies in patients dying of this disease, in which the thyroid gland was examined, striking and uniform disease of the gland was found in every instance; the pathological change consisting in the replacement of the glandular structure by fibroid tissue. Moreover, all clinical and pathological

observations up to the present date indicate that this is the one condition common to all cases of this disease.

Further valuable evidence of the active function of the gland is found in the recognition, in partial thyroidectomy, of an hypertrophy of the portion of the gland not removed, in a similar hypertrophy of the accessory glands or thyroid tissue in cases in which complete thyroidectomy has been performed experimentally in animals, and, finally, in the amelioration or arrest of sporadic cretinism, cachexia strumipriva, and myxœdema, which at present are regarded as practically identical, either by transplantation in animals or human beings, or by the injection of or feeding with a thyroid extract.

It will be of interest to refer briefly to a few of the experimental investigations upon which these observations are based.

Hofmeister (15) removed the thyroid gland in a number of puppies of five to sixteen weeks of age, allowing the accessory glands to remain. The usual fatal cachexia was averted and the animals were killed at intervals of one to seven months after operation, apparently in good health. At the autopsies a marked retardation of bony growth, as compared to that of the control animals, was found. The long bones and those of the pelvis were most affected; those of the cranium and jaw, least. The length of the tibial diaphysis, two and one-half months after operation, measured only fifty-eight millimetres, as compared with seventy-seven millimetres in the controls. There was also delay in the ossification of the epiphyseal lines and the synostoses. The sella Turcica was unusually broad, and the hypophysis cerebri (pituitary body) was noticeably hypertrophied. There was also a follicular hypertrophy of the ovaries. The retention of the accessory bodies, it is seen, was able to avert a fatal issue in extirpation of the thyroid. The presumably increased activity of their functions was not, however, sufficient to compensate fully for the loss of the gland.

Halsted, in a series of very interesting experiments, was able to demonstrate that many times the normal weight of the thyroid gland could be removed from the human subject by performing partial thyroidectomies at intervals of several months; in other words, that a very marked and rapid hypertrophy of the portion of the gland left, occurred (16).

In transplantation experiments, whenever successful fixation of the

gland has been obtained, amelioration of the cachexia has occurred. Among the earliest experimental workers in this field may be mentioned Schiff, Kocher, and Bircher.

A case of great interest of this kind has been reported very recently by Gibson (17). Apparent recovery from sporadic cretinism followed the grafting of one lobe of the thyroid gland of a sheep into the anterior abdominal wall and a second lobe into the abdominal cavity.

Gley's experiments on rabbits gave the following results: The removal of both the thyroid gland and accessory bodies was followed by death. Removal of the thyroid gland alone resulted in hypertrophy of the accessory bodies, with recovery. Removal of the accessory bodies alone was followed by no unfavorable results. Gley also found that extirpation of the spleen added neither to the rapidity of death nor to the severity of the symptoms. Removal of the hypophysis cerebri (pituitary body) produced symptoms similar to those observed after extirpation of the thyroid, and injection of thyroid juice cured or ameliorated the effects of such removal (18).

Upon the gradually acquired knowledge of the vital importance of a physiological activity of the functions of the thyroid gland rests the evolution of the present method of treatment of the diseases in which these functions are impaired or lost, viz.: Myxœdema, sporadic cretinism, and cachexia strumipriva.

A brief and necessarily incomplete sketch, through the limit of time permitted by the Association for the reading of individual papers, of the steps in this evolution may be of interest.

Historical Summary.

In September, 1882, Reverdin called the attention of the Medical Society at Geneva to the occurrence of myxœdematous symptoms after total extirpation of the thyroid in the human subject, calling the condition "myxœdema operatoire," and recommended that a portion of the gland be left in every operative case (19).

In April, 1883, Kocher reported a similar case to the Twelfth Surgical Congress at Berlin, giving to the condition the name "cachexia strumipriva" (20). In a personal letter to Horsley, he also stated that he transplanted in this year a small portion of a freshly excised goitrous gland, but the graft was soon absorbed (21).

In 1884, Schiff concluded that the thyroid was essential to the life of young dogs, and saved certain of them from the results of total extirpation of the gland and accessory bodies by grafting thyroid tissue previous to the operation (22).

In the same year Colzi transfused healthy blood into dogs suffering from the symptoms of cachexia strumipriva and succeeded in saving them. He believed that the function of the thyroid is to destroy or to prevent the accumulation of some deleterious substance in the blood, and that the symptoms are analogous to the uræmia following the removal of both kidneys (23).

In 1886, Rogowitsch observed trismus after total extirpation of the thyroid (24). Profound nervous disturbances, general fibrillar muscular tremor, tetany, trismus, etc., had been previously noted, under similar circumstances, by various observers. (Schiff (25), Wagner (26), Sanquirico and Canalis (27), Horsley (28), and Herzen (29).) The examination after death, in Rogowitsch's case, showed subacute parenchymatous encephalo-myelitis; and changes in the hypophysis cerebri indicating increased functional activity. In the experiment of transfusing the blood of an affected animal into a healthy one, Rogowitsch found no bad result. He states his opinion as follows: "The thyroid is an organ whose function is the removal or neutralization of certain products of tissue change, which products, if they accumulate in the blood, are very poisonous and destructive to the central nervous system and ultimately cause death. The hypophysis cerebri possesses a similar function, as proven by the above described changes in it after thyroid extirpation, and, also, as shown by its relative development in those animals which have a small thyroid."

In 1887, Munk found that by permitting the thyroid gland to remain *in situ* after shelling out each lobe from its bed and finally ligating all its vessels, he was able to preserve alive 20 per cent. of all the animals he subjected to this procedure.[1] The operation was practically total extirpation. In the light of later knowledge, we must believe that the preservation of life was due either to the presence of accessory glands or to the introduction into the circulation of the secretion which had accumulated in the gland (13).

[1] The subsequent history of these cases has not been published, as far as I am aware.

In March, 1887, Ewald reported that he had injected the expressed juice of the thyroid into dogs whose thyroid had been totally extirpated, and had obtained remarkable improvement of the symptoms (30).

A little later, Langendorff repeated the experiments of Ewald, with similar results (31).

Bouchard stated that in 1887 he had performed grafting experimentally in animals, and recognizing the fact that the juice contained in the graft was the essential feature, had made injections of the juice in the human subject with good results. These operations were not reported until 1892 (32).

In January, 1889, Heinrich Bircher, led by the results reached by Schiff, Ewald, and Colzi, performed grafting in a patient whose hypertrophied thyroid had been removed and who had serious nervous symptoms (convulsions, mental apathy, etc.), with excellent results. Three months later a relapse occurred and a fresh grafting was done with the result of maintaining perfect health for nine months, when a new series of epileptiform attacks appeared. The further history of this case does not seem to have been reported. In the same paper he notes three cases of compensatory hypertrophy of the accessory thyroid bodies, and one fatal case with tetanoid symptoms after removal of the thyroid for surgical reasons. Curiously, he recommended that this compensatory hypertrophy should be favored by having the patient drink water from districts in which goitre is notoriously prevalent (33).

In 1889, Kocher also grafted in five cases, with favorable results in at least one case (34).

The year 1890 was one of great activity in the direction outlined above, and the exact order of priority is difficult to determine.

Von Eiselsberg published quite early in the year the result of his experiments on animals, chiefly cats, in which tetanic symptoms invariably followed total extirpation, with results nearly always fatal. He found that if only four-fifths of the gland was removed recovery was possible; and, also, that after total extirpation the successful grafting of similar gland tissue prevented the fatal issue (35).

Horsley found that removal of the gland in monkeys was followed by myxœdematous symptoms instead of tetany, which he believed

to be due to the fact that the animals were kept continuously in a temperature of 90° F. after the operation (36).

In February, 1890, Horsley published a note on the possibility of the successful treatment of myxœdema, sporadic cretinism, and cachexia strumipriva by the grafting of thyroid tissue. He was not aware at the time that he had been anticipated in this direction by Bircher and Kocher, attributing the idea to Von Eiselsberg who, as has been shown, was not the originator of the substitution procedure (37).

In March, 1890, Lannelongue and Legroux grafted in a case of idiocy with "cachexia pachydermique" (sporadic cretinism?), with partial success (38).

In the first half of 1890, Bettancourt and Serrano, of Lisbon, in a case of cretinism of several years' duration, grafted with good results. The improvement was so immediate that they attributed it to direct absorption of the juice contained in the graft (39).

In September, 1890, Merklen grafted in the case of a myxœdematous dwarf, not idiotic, with the result of arresting a metrorrhagia of several months' duration, and producing an improvement in the other symptoms (40).

In the latter part of 1890, G. Vassale practised intra-venous injection of thyroid juice to preserve dogs from the effects of extirpation. In a total of eight animals, four recovered perfectly, three had relapses which yielded to a repetition of the injection but ultimately succumbed, and one died during the operation. In one of those which recovered the injection was not made until after the onset of the symptoms; in all the others the injection was made immediately after the extirpation of the gland (41).

In the early part of the following year, Gley confirmed the observations of Vassale by practising intra-venous injection of thyroid juice in dogs which were suffering from the effects of removal of the gland. He found that in a few minutes the nervous phenomena disappeared. Usually the symptoms returned on the following day, but yielded as before to a fresh injection. Recovery followed in every case in which the injection was made not later than twenty-four hours after the operation. He also found that it was not necessary to use juice obtained from the thyroid of a dog, but that the gland of a sheep served equally well (42).

The next, and clinically the most important, step in the evolution of the present method of treatment of myxœdema and sporadic cretinism was the employment of hypodermatic injections of an extract of the thyroid gland in the former disease, by Dr. George Murray of Newcastle, England, in 1891 (43).

At about the same time, Brown-Séquard and d'Arsonval (44) had suggested its use, but to Dr. Murray is due the honor of the practical application of the method and a demonstration of its success. Dr. Murray's first case, one of well-marked myxœdema, was treated with the most brilliant results by injections of a glycerin extract of the thyroid gland of a sheep, and others in rapid succession were treated similarly by him with equally remarkable benefit.

Numerous English clinicians quickly followed in his footsteps, and up to the present date sixty-seven cases of myxœdema and sporadic cretinism have been reported, of which a brief summary is appended, in which a similar method of treatment, or a modification of it to be described, has been followed by equally brilliant results. In these cases, with two exceptions, the myxœdematous symptoms not only have been greatly ameliorated, but in many they have disappeared, and individuals who had become apparently hopeless invalids, with degeneration of mental and physical vigor, have been restored to lives of comfort, and in some instances of usefulness.

A further evolution of this treatment is due to Dr. Mackenzie, of London, and Dr. Fox, of Plymouth, England (45). The disadvantages of injections of thyroid extract consist in the not infrequent production of abscesses and indurated swellings, presumably due to the use of not absolutely aseptic preparations, or to a technique not without reproach, and to the occasional occurrence of rather alarming symptoms immediately following the introduction of the extract into the economy—the result, Dr. Murray believes, of a too rapid injection.

By a curious coincidence, the discovery was made simultaneously by Dr. Mackenzie and Dr. Fox, that the administration by the mouth of the thyroid gland possessed all the advantages without any of the disadvantages of injections of the extract.

The raw minced gland of a sheep, prepared in various ways to make it as palatable as possible, was given at intervals of a day

or two to myxœdematous patients, with results similar to those described from the use of injections.

Further modifications of this treatment consist in the employment of the slightly cooked gland and of the extract in a dry state, in the form of tablets (46).

As the symptomatology and treatment of myxœdema, in addition to a consideration of the functions of the thyroid gland, have been assigned to me in the present discussion, I have thought that the former might be best illustrated by the clinical history of a typical case of the disease which has been under my personal observation for several months.[1]

It is as follows:

CASE.—S. W., housewife, forty-nine years of age, was admitted to the wards of St. Luke's Hospital, October 26, 1892.

Family antecedents: There is no evidence of the existence of myxœdema either in direct or collateral lines. The patient's father died of heart disease; her mother, of cancer of the breast.

Personal history: Menstruation appeared at fifteen years; the function was exceptionally normal throughout its entire period. The menopause occurred at forty years. There have been two births, at an interval of three years—the last twenty-five years ago, and no miscarriages. The patient's life has been throughout a tranquil and happy one. Exceptionally good health was enjoyed until about twelve years ago, when a slight impairment of hearing was noticed by the patient, which has gradually increased up to the present time. At about the same period the skin began to grow rough and scaly, and this symptom was more noticeable during the winter months. Very gradually the skin became dry and wrinkled, and there was little or no perspiration, even in warm weather.

Eight years ago a slight hesitancy in speech was appreciable, and gradually it became an effort to talk. About the same time the hair began to fall out, and no new growth followed. A little later a puffiness of the face, particularly about the eyes, was noticeable, which gradually increased until two years ago; since this date this symptom is said to have remained stationary. Six years ago locomotion became impaired, increased size of the feet was noticed, and larger and larger shoes gradually have been required. An apparent thickness of the tongue and enlargement of the hands, with brittleness of the nails, were next noted.

During the past two years there has been some impairment of memory. In the past year locomotion gradually has become very difficult, and of late the patient has been able neither to stand nor sit up without support, and

[1] The case was kindly referred to me by Dr. Elizabeth Cushier, of this city.

has been comfortable only when in bed. The eyesight, the sense of smell and of taste apparently have remained unaffected.

A study of the family and personal history of the patient throws little light upon the etiology of the disease. An inherited predisposition, catamenial disturbance, excessive childbearing or lactation, rapidly succeeding pregnancies, which have been regarded as possible factors in the causation of myxœdema, are all absent in the present case. This is also true as regards prolonged mental worry and specific or exhausting illnesses. The age at which the first symptoms were developed corresponds with that of a large proportion of cases of myxœdema, and the nature of the symptoms and the slow progress of the disease are very characteristic.

Condition on admission to hospital. The patient presents the characteristic appearance of an advanced case of myxœdema. The physiognomy is dull and mask-like, from the effacement of the natural lines of the face. The features are broad and course. The face is enlarged in all its dimensions, especially in its transverse diameter. Its skin is dry, wrinkled, and markedly thickened, especially over the forehead. Over the cheeks and bridge of the nose there is a rather sharply defined pinkish patch, in strong contrast with the porcelain-like hue of the orbital area. The lower eyelids are swollen and baggy, and a puffiness of the tissues immediately below is very noticeable. The whole nose is swollen, and the bridge flattened. The hair of the eyebrows and eyelashes is short and scanty. The apertures of the eyes are narrowed and the space between them is broadened. The mouth is widened transversely. The lips are swollen, especially the lower one, which is pendulous, everted, and of a violent hue. There is a constant dribbling of saliva. The mucous membrane of the mouth is evidently thickened, the tongue markedly so. The gums are swollen and spongy. The teeth which remain, sixteen in number, are in various stages of decay. The uvula is normal in appearance. The scalp is covered with a thick mass of dry scales, and the hair is dry, ragged, brittle, and scanty. There is an extensive tumefaction of the subcutaneous tissues directly above the right ear. The skin of the trunk and extremities, particularly of the hands and feet, is excessively dry, thickened, and scaly. There is an entire absence of hair in the axillæ and about the pubes. The hands and feet are markedly thickened and broadened. The nails are brittle, marked with longitudinal striæ, and the crescents are absent. There is slight pitting on firm pressure over the dorsal surface of the feet. Circumscribed tumefactions are present in both supra-clavicular regions, this sign being more marked on the right side. The speech is monotonous, slow, and of a character which must be heard to be fully appreciated. It is characteristically similar in all the cases of myxœdema which have come

under my notice. A slowness in apprehension, thought, and action is very appreciable, but the mental process finally is correctly performed. There is some impairment of memory, especially for recent events, and the patient is emotional. There is a paresis of the nuchal muscles, of the muscles of the trunk and of the extremities. The head tends to fall forward, the patient sits up with great difficulty, and cannot stand or walk without much assistance. There is, in addition, a certain amount of incoördination of the muscles of the lower extremities. Dynamic register of grip: right, 71; left, 68. There is a distinct diminution in the reaction to the faradic current in the muscles of the extremities. The reaction of degeneration to the galvanic current is not present. Cutaneous sensation is in all respects apparently normal. Retardation of sensation is absent. The deep reflexes are normal, the cutaneous diminished. There is incontinence of urine and obstinate constipation, with, from time to time, involuntary movements of the bowels. The urine has a low specific gravity (1012–1014), and is, as a rule, alkaline in reaction. It contains a trace of albumin. Sugar is absent. Amorphous and triple phosphates are very constantly present. The average excretion of urea is four grains to the ounce. The eyesight is apparently normal, as are also the senses of taste and smell. The hearing is markedly impaired. The voice is only heard when greatly raised and the mouth placed close to the ear. An examination, kindly made by Dr. Charles S. Bull, is as follows: Tuning-fork heard equally well in both ears. Watch slightly better in left ear, but heard only when in contact with auricle. Membrana tympani in each ear shows the usual signs of chronic catarrhal proliferous otitis. They are sunken and altered in curvature, particularly in Shrapnell's membrane. Handle of malleus very prominent in both ears. Light spot somewhat diffused. Eustachian tubes readily opened by politerization. There is chronic antero-posterior hypertrophic rhinitis, which extends well down into pharynx. The temperature is constantly subnormal, the range being from 96° to 97.5° F. (mouth). In connection with the low temperature noted, it may be stated that the patient says she is always cold, even in hot weather; moreover, that there is never any moisture of the skin at any season of the year. The pulse averages about 70 and is without tension. There is no appreciable thickening of walls of arteries. Examination of the blood shows good rouleau formation. The red corpuscles are of average size and shape. Hæmoglobin, 48 per cent.; red cells, 3,160,000 per c.mm.; white, 4,680 per c.mm. The white cells are absolutely but not much relatively reduced. Stained specimens show various forms of white cells in their normal proportion to each other. (Dr. Southworth.)

Physical examination gives negative results as regards the lungs, liver, and spleen. The first sound of the heart is feeble; there is an absence of murmurs. There is no enlargement of the superficial glands. There are a number of deeply pigmented moles scattered over the surface of the trunk, extremities, and neck. The thyroid gland is not palpable; the fulness of the neck, however, interferes with a satisfactory examination.

The symptoms and signs presented by the patient form an almost classical picture of myxœdema.

The long duration of the disease—twelve years—the gradual evolution of symptoms, the final development of the stage of degeneration, which justly occasioned doubt, on the admission of the patient to the hospital, of a much further prolongation of life, constitute a very interesting and instructive study.

As the history of the case is intended to embrace the symptomatology of myxœdema, I shall call attention only to those symptoms which were *not* observed in the present instance, but which have been reported as being present with more or less frequency in other cases, and to those which *were noted* and which hitherto either have not been described, or have been mentioned as of infrequent occurrence.

Insanity (melancholia, dementia) has been noted not infrequently associated with myxœdema, and at least one case of melancholia with epilepsy has been reported (47).

Its possible dependence in such instances upon the myxœdematous state apparently had not been entertained previous to the results observed by the present method of treatment of the latter disease. A further reference to this point will be made later.

In the present case, no disturbance of the psychical functions other than that mentioned existed.

Retardation of sensation, which has been observed in about half of the recorded cases of myxœdema, was not present.

In regard to this symptom, it may be mentioned that in many cases the note of the reception of the sensation may have been deferred by the hebetude of the patient.

Incontinence of urine, which was observed in the present case, has occasionally been noted in others. Incontinence of feces, which was also present, has not been reported hitherto, so far as I am aware.

The case seemed an exceptionally favorable one, from its long duration and the advanced and degenerative stage which it had reached, for a study of the effect of treatment by feeding with the thyroid gland.

Feeding, rather than injections of the extract, was determined upon, on the ground that any benefit which might ensue would be even of greater interest. In spite of Mackenzie's reported results, much skepticism was felt of the possibility of a remedial action of a

gland secretion, which could only enter the blood or lymph channels after its introduction into the stomach and its exposure to the action of the gastric juice.

From the date of admission to the hospital until November 26th—one month—the patient was confined to her bed without treatment of any kind, that the effect of an equable temperature and simple hygienic measures might be observed. During this period her condition remained without appreciable change. The temperature (mouth), taken at intervals of four hours, except during sleep, presented slight diurnal variations, the range, as a rule, being between 96° and 97° and a fraction.

FIG. 1.

Immediately before beginning treatment.

On November 26th a sandwich, of what at the time was supposed to consist of the minced raw thyroid gland of a sheep, was given and repeated on the six succeeding days. Its ingestion was not followed by the slightest variation in the temperature curve, the percentage excretion of urea, or in any subjective sensation. It was then discovered that a large lymphatic

gland, taken from the tissues immediately contiguous to the site of the thyroid, had been used instead of the latter.

On December 10th half a drachm of the minced raw thyroid gland of a sheep, in an equal amount of glycerin, was given by the mouth. The temperature, pulse, and urea excretion were alike unaffected by its administration. A like amount was given on the four succeedings days, with similar results. The only subjective sensation complained of by the patient during this period was a slight feeling of dizziness.[1]

On December 15th one drachm of the raw minced gland was administered in a similar amount of glycerin. The pulse, respirations, and temperature immediately previous were 72, 16, and 97° respectively. Five hours later the pulse and temperature were 76 and 98.5°, the respirations remaining unaffected. The patient expressed herself as feeling no discomfort of any kind. A similar amount of the gland was given daily with a single omission until January 7th—twenty-three days.

The temperature range during this period was between 98° and 100.2°, the higher point being reached in the afternoon. The pulse rose to 96 on the second day, and constantly ranged from this date between 90 and 106. The respirations were also increased in frequency—20 to 26. It is seen that with the administration of the increased dose the pulse, temperature, and respirations were immediately affected. The urea excretion also rose directly from 3½ grains to the ounce to 8 grains.

On December 29th, nineteen days after the first dose of the gland had been given and two weeks after its use in larger amounts, the improvement in the patient's condition was very striking. The expression of the face had changed very remarkably; the swelling of the tissues had greatly diminished; the bagginess of the lower eyelids had disappeared; the lower lip was no longer everted and swollen; the saliva had ceased to dribble; the speech had markedly improved, and the thickness of the hands and feet had begun to diminish; the tumefactions above the ear and in the supra-clavicular regions were not palpable; the skin of the palms of the hands and of the feet was distinctly less dry; the scanty hair on the scalp, however, had become still scantier; the reaction of the urine was still alkaline, of low specific gravity, and contained rather a large amount of phosphates.

The patient expressed a feeling of great comfort, and, moreover, a sensation of general warmth which she had not felt for years, and which had been developed at the very beginning of treatment.

The raw gland had, however, become very distasteful, and she could be persuaded only with difficulty to take it.

On January 7th, after twenty-three days of its use, its ingestion was followed by vomiting and a rather acute disturbance of digestion, and the treatment was discontinued for ten days. The improvement in the patient's general condition was, however, uninterrupted during this period. It was

[1] The preparations used by me were kindly furnished by Dr. Paul Gibier and Dr. George Crary, of this city.

noted that the temperature curve rapidly lost its irregularity on the temporary discontinuance of the treatment and became normal, and the pulse gradually fell to 76 to 80.

FIG. 2.

On the twenty-first day of treatment.

On January 16th, five weeks after the first ingestion of the raw gland, the following note was made:

The patient is hardly recognizable as the one of a month ago. The myx-

œdematous signs, as far as the face is concerned, have entirely disappeared. The expression is natural; there is no longer any appreciable swelling or increased thickness of the skin of the face, neck, or trunk, of the lips or tongue. The speech has lost its peculiar characteristics. The hearing has so much improved that the patient now hears the ordinary conversational

FIG. 3.

Eighteen weeks after treatment was begun.

voice across the ward, and also the singing in the chapel of the hospital, 150 feet distant. The dryness of the skin has markedly diminished, and beginning desquamation of the hands, feet, and scalp is noticeable. The hands have recovered their normal size, and the feet are markedly thinner. An abundant new growth of fine hair on the scalp and eyebrows is appreciable. With the disappearance of the fulness of the neck, a satisfactory examination is possible. The thyroid gland is not appreciable.

On January 19th the treatment was again initiated and has been continued to the present date. A slight change has been made in its technique and in the dosage. The expressed juice of the gland, rather than the raw substance, has been given, as the former is without taste when administered in milk or water, and does not produce any digestive disturbance. Fifteen minims of the juice, representing one-quarter of an average amount obtained from one lobe of the gland of the sheep, has been given once weekly, by the mouth, in a little milk. The improvement has been continuous.

During the first week in February desquamation of the skin of the entire body occurred; very large strips, several inches in length and breadth, could be easily removed from the different areas. The process was very rapidly completed, leaving a delicate, elastic, normally moist skin, and of a natural color. The entire scalp became thickly covered with a new growth of hair, and the same was true of the eyebrows. A new growth about the pubes was also noticeable. During the early period of the treatment the hair of the scalp which still remained rapidly fell out. The patient became cheerful, bright, and the improvement in the mental processes was very marked. Gradually the patient became able to sit up without support, and then to stand and finally to walk. It will be recalled that on admission she had been practically bedridden for a year.

A study of the photographs taken before treatment and at subsequent intervals will illustrate the almost marvellous change which has been effected in the patient's appearance and condition.

The similar clinical observations which have now been made by many careful investigators, have secured for the method of treatment which I have described not only a very general recognition, but they naturally have suggested therapeutic possibilities which hitherto have hardly been dreamed of. The field of study and investigation thus opened is a wide and most interesting one. The future history of the cases of myxœdema and sporadic cretinism, which are reported in the present paper, will be watched with interest. Present indications suggest the possibility that the maintenance of the extraordinary improvement noted may be secured only by the indefinite continuance of the treatment. A study of the appended tables reveals the interesting fact that insanity was present in five of the cases. In three of these complete cure is reported, in one marked improvement, and in one case cure followed by a slight relapse.

In conclusion I will offer a few suggestions in regard to the technique of the treatment. From my personal experience, I believe that the best form in which to administer the gland is the expressed juice given in a little milk or water. Dr. George Crary, of this

city, has found the size and weight of the lobes of the sheep to vary so widely, that he has been led to adopt a uniform standard for the preparation of the juice, viz., one of which one drachm of the glycerin extract represents grains xxiv of the gland. At the beginning of treatment in any given case, minims xv of this preparation should be given daily and its effects carefully watched. If no effect is obtained, the dose should be doubled and still further increased if necessary. As improvement occurs, smaller doses and given at longer intervals, will be found sufficient to secure further good results, until finally minims x–xv, administered no oftener than once a week or even at longer periods, will be indicated. During the first weeks of treatment, experience suggests the wisdom of carefully guarding against possible ill effects, such as symptoms of heart failure, etc., by insisting upon the avoidance of all physical exertion on the part of the patient.

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Cases of Thyroid Grafting.

Reporter.	Sex and age.	Previous condition	Method	Results.	Reference.
Kocher,	1. Not stated	....	Implantation of small portions of goitrous gland.	Speedy absorption.	Brit. Med. Journ., July 26, 1890, p. 201.
	2 cases	.....	½ gland grafted into abdominal wall.	Aseptically exfoliated.	
	3 cases	.....	Whole gland inserted loose into abdominal cavity.	One case greatly improved.	
Bircher,	F. 33	Epileptiform seizures after accidental total extirpation of thyroid.	Intra-peritoneal graft of portions of apparently normal human thyroid.	Cure; relapse after three months; fresh grafting nine mos. later; second relapse.	Volkmann, Samml. klin. Vorträge, March 5, 1890, No. 357.
Lannelongue and Legroux,	F. 14	Cretin; idiotic; thyroid apparently absent.	⅔ of one lobe of sheep's thyroid into right submammary region.	Result not reported.	Soc. de Biol., Mar. 8, 1890.
Bettancourt and Serrano,	F. 36	Myxœdema for several years; no thyroid perceptible.	½ sheep's gland inserted into each submammary region.	Immediate and marked improvement in physical condition; mental condition not stated.	La Semaine Méd, Aug. 13, 1890, p. 294.
Merklen,	F. 41	Myxœdema for ten years; mental condition fair; metrorrhagia.	1 lobe of sheep's thyroid into submammary region.	Cessation of metrorrhagia: improvement of myxœdema	Mercredi Méd., Nov. 19, 1890, p. 571.
Macpherson,	F. 39	Myxœdema three years; melancholia; stupor; delusions of fear.	Portions of sheep's gland into each submammary region.	Cured.	Edinb. Med. Journ. May, 1892.
Robin,	M. 7	Congenital myxœdema.	Two lobes from sheep into submammary region.	Had previously been treated successfully by injections of thyroid juice; grafting done to perpetuate effect.	Lyon Méd., Aug. 7, 1892.
Gibson,	M. 6	Sporadic cretinism	Two lobes from sheep into pectoral region. Ten months later, two lobes into abdominal cavity.	Very marked improvement after first operation; myxœdema cured; cretinism lessened.	Brit. Med. Journ., 1893, vol. i. p. 58.
Affleck,	1 case	Sporadic cretinism	Grafts into mammary region.	Very much benefited	Lond. Med. Press, Feb. 22, 1893, p. 200.

Cases Treated by Injections.

Reporter.	Sex and age.	Duration of disease.	Method.	Duration of treatment.	Results.	Remarks.	Reference.
G. R. Murray,	F. 46	4–5 yrs.	Glycerin extract of half sheep's gland twice per wk.	3 mos.	Very much improved.	Relapses when treatment is discontinued.	Br.Med.Journ. Oct. 10, 1891, p.746; Aug.27, 1892, p. 449.
G. R. Murray,	F. 52	12 yrs.	Glycerin extract of half sheep's gland once per week for 4 months, each second week for 3 months.	7 mos	Improved very considerably.	.....	Br.Med.Journ. Aug. 27, 1892, p. 450.
G. R. Murray,	F. 62	6–7 yrs.	Glycerin extract of half sheep's gland each week.	.....	Very marked improvement.	Sudden death from heart-failure after exertion.	Ibid.
G. R. Murray,	F. 64	5 yrs.	Glycerin extract of ¼ to ½ gland each week.	3 mos.	Considerable improvement.	Death from sudden heart-failure.	Ibid.
A. T. Davies,	M. 43	13 yrs.	Murray's method.	About 7 mos.	Remarkable improvement.	Relapses when treatment is discontinued.	Ibid.
A. T. Davies,	Not stated	Not stated.	Murray's method.	Not stated.	Gradual improvement.	.....	Ibid., p. 451.
C. F. Beadles,	F. 50	8 yrs	Injections at various intervals—in all 19	5 mos.	Insanity cured physical symptoms practically cured.	Form of insanity: delusions and religious melancholia.	Ibid., Dec. 24, 1892, p. 1386.
Hearn,	1	.....	No details.	.....	Improved very much.	.....	Ibid., Aug. 27, 1892, p 452.
	2	.....	" "	.....	" "		
	3	.....	" "	.....	" "		
E. C. Carter,	F. 43	More than 5 yrs.	Murray's method.	3½ mos.	Insanity improved; physical symptoms cured.	Form of insanity: melancholia with paroxysmal excitement.	Ibid, Apr. 16, 1892, p. 805.
W. Beatty,	F. 45	5–6 yrs.	Murray's method	2 mos.	Practically cured.	....	Ibid., Mar. 12, 1892, p. 541.
Mendel,	F. 58	11 yrs.	Injections daily.	1 mo.	Much better physically and mentally.	Marked mental apathy.	Deut. Med. Woch., Jan. 13, 1893
Napier,	F. 54	5 yrs.	At various intervals, sixteen in all.	6 wks.	Much improved.	.....	Glasgow Med. Journ., Sept. 1892, p. 161.
Claye-Shaw,	F. 33	4 yrs.	Thyroid juice.	3 mos.	Quite well in all respects; insanity cured.	Form of insanity: restless melancholia almost homicidal.	Br.Med Journ. Aug. 27, 1892, p. 451.
Mitchell-Clark,	M. 48	Not stated.	Murray's method.	2 mos.	No result.	.....	Ibid.
Mitchell-Clark,	Middle age.	Not stated.	Murray's method.	6 wks.	No result.	.....	Ibid.
Robin,	M. 7	Congenital.	Daily injections of thyroid juice.	Not stated.	All traces of œdema disappeared; other symptoms improved.	Grafting done subsequently to perpetuate effect.	Lyon Méd., Aug. 7, 1892.
Henry,	F. 44	14 yrs.	Bi-weekly for ten weeks; weekly for eight weeks.	18 wks.	Vastly improved.	Subsequently treated by thyroid feeding.	Br.Med.Journ. Apr. 8, 1893, p. 737.

CASES TREATED BY INJECTIONS—*continued.*

Reporter.	Sex and age.	Duration of disease.	Method.	Duration of treatment.	Results.	Remarks.	Reference.
H. Fenwick,	3 cases	.....	.....	.....	Improvement.	No details given.	Ibid., Oct. 22, 1892, p. 894.
Ruffer,	2 cases	.....	.....	.....	Apparently cured.	No details.	Ibid.
Hadden,	2 cases	.....	.....	.....	Not stated.	No details.	Ibid.
Bouchard,	2 cases	.....	.....	.....	Rapid improvement.	.....	Bull. de Méd., Oct 2, 1892.
Barron,	F. 64	5 yrs.	Two injections per week.	About 3 mos.	"Considers herself well."	.....	Br. Med. Journ. Dec. 24, 1892, p. 1384.
Barron,	F. 55	Not stated.	Two injections per week.	7 wks.	Very much improved.	Under treatment at date of report.	Ibid.
Cockhill,	F. 32	4 mos.	Injections three times a week.	2 mos. ?	Cured.	Thyroid was enlarged instead of atrophied.	Ibid., Jan. 7, 1893, p. 8.
Lundie,	F. 54	1½ yrs.	Murray's method.	6 wks.	Improved.	Treatment discontinued on account of abscesses; subsequently treated by thyroid feeding.	Ibid., Jan 14, 1893, p. 64.
Wichmann,	F. 35	2 yrs.	Glycerin extract of nine glands in all.	5 wks.	Cured; subsequently relapsed to a slight degree.	Form of insanity: hypochondriasis and melancholia.	Deut. Med. Woch, Jan. 14, 1893, and Mar. 16, 1893
Wichmann,	F. 36	4 yrs.	Glycerin extract.	2 mos.	Cured; symptoms of slight relapse six weeks later.	.....	Ibid.. Mar. 16, 1893.

Cases of Thyroid Feeding.

Reporter.	Sex and age.	Duration of disease.	Method.	Duration of treatment.	Results.	Remarks.	Reference.
Mackenzie,	F. 39	4 yrs.	Raw thyroid and glycerin extract.	3 wks.	Marked improvement.	.....	Br. Med. Journ. Oct. 29, 1892, p. 940.
Fox,	F. 49	Not stated.	Glycerin extract, and subsequently gland lightly cooked.	3½ mos.	Cured.	.....	Ibid.
Bramwell,	F. adult	Not stated.	½ gland on alternate days at first, and smaller doses subsequently.	Not stated.	Very much improved.	Produced symptoms of heart-failure at first.	Ibid., Feb. 25, 1893, p. 411.
Foulis,	Not stated	.....	⅛ thyroid.	.....	Death by violent diarrhœa after 1st dose.	.....	London Med. Press, Feb. 22, 1893, p. 200.
	Not stated	.....	⅛ thyroid twice per week.	8 wks.	Greatly benefited.		
Baber,	M. 53	6 yrs.	1 gland at irregular intervals, in all 5 glands.	.....	Marked improvement.	.....	Br. Med. Journ. Jan. 7. 1893, p. 10.
Lundie,	F. 54	16 yrs.	⅙ gland twice per week.	.....	Cured.	Previously treated by injections.	Ibid., Jan. 14, 1893, p. 64.
Holman,	F. 44	7 yrs.	.....	.....	Practically well.	Still under treatment.	Ibid., Jan. 21, 1893, p. 114.
Davies,	4 cases	.....	.....	.....	Improved rapidly.	Heart-action extremely enfeebled in one case by the remedy.	Ibid., Feb. 4, 1893, p. 252.
Calvert,	1 case	.....	Fried gland.	.....	Vastly benefited.	.....	Ibid., p. 235.
Pasteur,	1 case	.....	.....	.....	Much benefited.	.....	Ibid.
Mackenzie,	F. 40	.....	.....	.....	Practically well.	.....	Ibid., Mar. 4, 1893, p. 461.
Hadden,	1 case	.....	Powdered thyroid extract.	1 mo.	Quite well.	.....	Ibid.
Benson,	Mid. age	8 yrs.	Thyroid extract twice daily.	3 mos.	Nearly well.	... .	Ibid., Apr. 15, 1893, p. 795.
Henry,	F. 44	14 yrs.	One lobe every second day.	.....	Vastly improved.	Previously treated successfully by injections.	Ibid., Apr. 8, 1893, p. 737.
Vermehren,	F. 29	24 yrs.	Powdered extract.	.....	Marked improvement.	.....	Deut. Med. Woch., Mar. 16, 1893, p. 255.
Laache,	M. 49	1 yr.	Powdered extract.	3½ mos.	Cured.	.....	Ibid.
Howitz,	E. 42	7 yrs.	4 lobes from calf daily for one month; subsequently 2 lobes every second day.	.....	Much improved.	.....	Ibid.
Shapland,	F. 52	10 yrs.	½ thyroid daily slightly cooked.	3 mos.	Quite well.	.....	Br. Med. Journ. Apr. 8, 1893. p. 738.
Thompson,	5 cases	.....	¼ gland once per week.	.....	In 7 weeks had grown 1¼ in. general condition much improved.	.....	London Med. Press, Feb. 22, 1893, p. 200.
	M. 18	.....	" "	.....	In 8 weeks grew 1¼ in.		
Bruce,	1 case	.....	.....	.....	Cured.	No details.	Ibid.
Dunlop,	5 cases	.....	.....	.....	1 improved; 4 not stated.	.....	Ibid.
Church,	2 cases	.....	.....	.....	Not stated.	No details.	Ibid.

CASES OF MYXŒDEMA AND ACROMEGALIA TREATED WITH BENEFIT BY SHEEP'S THYROIDS.

Recent Observations Respecting the Pathology of the Cachexias following Disease of the Thyroid; Relationship of Myxœdema, Graves's Disease and Acromegalia.

By JAMES J. PUTNAM, M.D.,
of Boston.

Case I. is that of an unmarried lady, now forty-eight years old, and always of delicate health.

I was first called to see her in December, 1885, and at the time of my visit the diagnosis was beyond question, even from her appearance alone.

She had taken cold while menstruating during a visit to the Philadelphia Exhibition of 1876, and it is probable that the myxœdematous symptoms began at about this time; some of them, perhaps, even earlier. She had always been pale, and slow in movement. The family history on the mother's side was markedly neurotic.

The face was clayey-gray, with a yellowish tint, the skin thick, stiff, dry, and coarse. The lips were protuberant and thick, and moved each in one piece, as it were, as she talked. The eyelids were swelled and alabaster-like in appearance, especially the upper, which overhung the eyes so that at times she had to throw the head back a little in order to see. The neck was thick, the hands were large, scaly, and dry, and a similar dry and coarse condition of the skin was everywhere present.

The nutrition of the teeth and nails was defective, and the hair had fallen out except for a few bunches here and there.

Formerly slender and with delicate coloring, she now looked overgrown and old. The limbs were large but not strong, and the skin was so inelastic and so tightly stretched over the legs below the knee, that the masseuse found it impossible to use the ordinary methods of manipulation. No true œdema was noted at this time, but at a later period the ankles pitted deeply on pressure. The swelling of the eyelids was partly watery, and increased during the night toward the side on which she lay.

The pulse was but 60; the heart-sounds free from murmur, but exceedingly feeble. There was a tendency of the head to droop forward, so that it was with an effort that she held it erect. The voice was husky and the tongue thick. The gait was slow and insecure, so that she often stumbled and sometimes fell. She felt weak, and became breathless on slight exertion.

The mental condition was no less striking than the physical. An inconquerable inertia and apathy imprisoned her thought, feeling, and action, so that she could neither plan nor execute effectively, and every trifling duty seemed a mountain to climb; and yet her ineffectiveness did not fill her with real despondency.

Her friends would leave her with one boot on and the other in her hand, and return an hour later to find her in the same condition and attitude. Or what she held would slip from her grasp and she would not stoop to pick it up. Or, at times, she would lean in a stupor against the mantel-shelf, and remain motionless for one or two hours. The nearest duties often passed unfulfilled, and the thought of them failed to rouse her. Yet in spite of her slowness, and lethargy, and lack of initiative, she was neither melancholic nor demented, and would converse intelligently and pleasantly, though without animation, on many subjects. It is interesting to note (see below) that a certain degree of this apathy and slowness was characterstic of her temperament even many years before her illness began.

She slept all night, though often troubled with distressing dreams, but was constantly drowsy in the day. She suffered much from constipation, and later from hemorrhoids, and had an offensive expectoration, which no doubt contributed to give the breath the cadaveric odor which then characterized it.

The menstruation was at that time regular, but profuse; later it became very irregular, and was absent for months together, and her periods would leave her much weakened.

The urine was habitually very pale, and of low sp. gr,, free from albumin and sugar. All the solid constituents were diminished, the amount of urea being 11.78 grm. to the litre (Prof. E. S. Wood).

The thyroid could not be felt. The skin was cool to the touch; and the temperature usually ranged around 95° F. Several times it almost touched 94°; and 97° was rarely, if ever, passed, even in slight sickness.

Blood-counts made during March and April, 1886, showed 3,120,000; 3,200,000; 3,234,000; 4,240,000. The proportion of whites was normal.

The next four years brought little change, except that in winter she would be worse, in summer better.

In the summer of 1891, however, a new symptom showed itself, namely, a synovitis with great external swelling, first of one knee, then of the other, brought on by a trifling shock or wrench, due to stepping heavily, the first time out of a carriage, the next time out of a horse-car. In one of the cases reported very early by Dr. Ord, the rupture of both patella tendons occurred in a similar manner, and the excessive swelling has been several times ob-

served. The synovitis ran a very indolent course, and the appearance of the knee, with its thickened tissues, was so peculiar as to suggest the presence of some other process than simple effusion.

Up to the 1st of June, 1892, no treatment had brought material benefit, though persistent massage had given the patient much comfort. In June, 1892, I began a series of tri-weekly injections of a glycerin and carbolic extract of the sheep's thyroid, prepared as recommended by Dr. Murray.

Slight signs of improvement began to show themselves by the end of one or two weeks. In the course of six weeks the improvement in color, strength, and manner attracted the attention of everyone who knew her, even the children of her neighborhood, and was further confirmed by the appearance of a growth of fine hair all over the head, and a marked rise in pulse and temperature.

The temperature varied, but by the end of August, perhaps earlier, it ranged pretty constantly between 96° and 97° F. Menstruation, which had been absent so long, recurred in July, August, and September, but such recurrences had occasionally happened, and it was still profuse and painful.

The swelling of the eyelids varied in amount, but during August it was almost absent, and that of the ankles had greatly lessened.

With the advent of the colder weather of September and October, I saw with regret that her improvement, hitherto steady, seemed to have suffered a check. She began to look pale and to feel languid, the swelling of the eyelids reappeared, and she complained of pain in the chest on slight exertion. Attributing this in part to an interruption of the treatment during the first ten days of October, I tried giving the injections more frequently than ever, part of the time almost daily, though at first without marked effect.

In November she began the treatment by the mouth, as recommended by Mackenzie and by Howitz, of Copenhagen, and took five or six sheep's thyroids a week (or more strictly, five or six lobes, as the sheep's thyroid consists of two separate lobes).

During the next month, and even after the final stage of improvement had been fairly entered upon, she complained much of a sense of thumping in her head, and while her mental condition was becoming steadily more natural, her appetite and strength seemed for a time rather to fail.

Ever since the outset of the treatment, she had noticed at times a sense of flushing and dizziness after the injections, such as has been noted in the reports of some of the English cases, but neither this effect nor the increased secretion of urine which others have noted was at all striking.

On December 9th, an estimation of the hæmoglobin by Fleisch's apparatus gave 55 per cent. Toward the end of December there was another period of depression in which she complained of increased thumping in the head and ears, and of nausea and languor, especially in the morning. These symptoms seemed at least partially attributable to an excess of thyroids, of which she had taken four glands a week, though these periods of depression did not invariably attend the use of the larger amounts.

This sense of illness was, however, attended by a rise of pulse and temperature rather than a fall, the pulse reaching 78 on December 18th, and the temperature 98°. And furthermore, it was plain that the whole character of her nutrition was becoming more normal, though it was not in all respects satisfactory. On December 21st, when I had not seen her for nearly three weeks, it was evident at the first glance that the condition of myxœdema was giving place to one of simple anæmia. She complained a great deal at this time of itching, which others have noticed likewise, perhaps from the action of the thyroids, but more probably from the changes taking place in the skin.

It was difficult to say whether she had actually grown paler or less pale, so unlike was her present complexion to that of the clay-like mask that she had worn so long. Unfortunately, she could not easily be weighed, but it was clear that she was rapidly growing thinner and slenderer, while her hands were becoming softer and more shapely. The clothes that she had worn were now hanging in folds, and in fact she became at this time really too thin, and with still further improvement she has gained flesh somewhat.

The opening of the new year was marked by her discarding her wig in favor of her new growth of dense and soft hair (now about four inches long) and by her beginning to take the thyroids in the form of powder, skilfully prepared by Parke, Davis, & Co., at my suggestion.

I had been in correspondence with them for this purpose for a number ot weeks, and did not learn until later that similar methods were being adopted in Sweden and England. Fifteen grains of this powder represents one lobe of a sheep's thyroid. The taste is found nauseous by some patients, and does not disappear for many hours. These objections are mainly obviated by the use of capsules, or "enteric" pills, which do not dissolve in the stomach.

Not only had her face and figure by this time changed so that acquaintances occasionally failed to recognize her, but her voice had grown markedly firmer and clearer, and her manner alert and responsive.

An accurate examination of the blood made by Dr. J. J. Thomas gave the following result:

Reds . .	5,700,000	Polynuclear whites	66.4 per cent.
White . .	7,000	Mononuclear " .	21.6 "
Hæmoglobin	61 per cent.	Lymphocytes . .	10.04 "
Proportion of white	1:800	Eosinophiles . .	2.0 "

No increase in size of reds. A few myelocytes.

The menstruation recurred normally and almost painlessly in January, February, March and April, appearing exactly at the expected date. For two weeks in February and March she took no thyroids, and toward the close of that time there were signs of a recurrence of symptoms, a firm non-œdematous swelling appearing in the legs above the ankles. The mental condition remained good, and on resumption of the thyroid powders the slight swelling soon disappeared.

Since the treatment was begun, the neck, waist, and arms have diminished about three inches in girth, and the old shoes and gloves have, so to speak, discarded themselves. She is still an anæmic and delicate person, as she always was, but as regards any distinct myxœdema she is practically well.[1]

The temperature is usually normal, but occasionally runs half a degree too low.

CASE II. is that of a lady fifty-five years old, and is particularly interesting, both because the improvement was very rapid, and from the fact that previous to the onset of the myxœdematous symptoms the thyroid was much enlarged, and that moderate but constant tachycardia was present. The patient has been under the care of another physician, and I have seen her only incidentally, except during the first period of the disease, when I tried for some time to reduce the size of the goitre by electrolysis. The case is also of interest from the fact that the patient's cousin and aunt had myxœdema in a pronounced form, and eventually died with it, the latter as an elderly person, the former in middle life. The aunt had been for many years crippled with rheumatoid arthritis. Though the patient had led an active life, she had been anæmic and had suffered much from palpitations in childhood and adolescence.

The case seems to be one of those where an exciting cause of the disease may well have been anxiety and emotion, acting on an intense and sensitive temperament. The thyroid first began to enlarge about ten years ago. The tumor was unusually hard, much harder than the normal gland, and there were no vascular murmurs such as are often seen in Graves's disease. There was no exophthalmus,[2] but the pulse was always moderately rapid—from ninety to one hundred and twenty. In view of the important question as to the possible relationship between Graves's disease and myxœdema, it is interesting to bear in mind that we have here a case where, in the presence of a manifestly hereditary tendency to myxœdema, the first actual change was this thyroid disease, with at least one of the Graves's disease symptoms. (Perhaps, however, the tachycardia was purely reflex. See below.)

It is also a noteworthy fact that the patient's health failed considerably during the first period, and that besides dyspnœa, which may have been due to pressure, she suffered much from anæmia and debility. As her health had previously been fairly good it is reasonable to suspect the thyroid disease as having been responsible for the falling off at this period, the more so that with the

[1] An examination of the blood made since this paper was written has shown that the anæmia has not improved of late, but rather grown more severe, though in other respects the patient is doing well.

[At the present time, which is about six weeks since this foot-note was written, the patient reports herself as doing well in all respects. An interesting point has shown itself with relation to the question of dose. The patient, namely, had been taking a capsule containing two and a half grains of thyroid powder every day. Although in most respects she did pretty well with this, it was evidently not quite enough, because a slight but well-marked œdema of the eyelids gradually made its appearance.]

[2] This is doubtful. One of her physicians thought it was present.

recent thyroid treatment not only the myxœdema but also the anæmia has for the most part disappeared. The myxœdematous changes first showed themselves two years ago, at the time of the menopause, and have been unmistakably characteristic; the presence of the alabaster-like swelling and pallor of the eyelids, lips, and face, the dryness of the skin, the increased size of the hands, the gross enlargement of the body, slightly subnormal temperature, thickness of the tongue, and slow speech leaving no doubt as to the diagnosis. The urine contained a trace of albumin, and occasionally a few casts. Mental changes have not been present.

The treatment with the thyroid powder was begun about February 15th, since which time the patient has taken one powder of fifteen grains, which is the equivalent of one lobe of a sheep's thyroid, every second day.

The improvement was more rapid than in the first case, perhaps because the disease was less advanced and because the patient's previous health had been better. There is still some swelling of the legs, with ordinary œdema, but the patient's face has regained its delicacy and size and color of fifteen or twenty years ago. The thyroid is still large, though not so large as before. It will be very interesting to follow the condition of the urine in order to see whether the renal changes disappear. At present casts are still to be found, though they were absent in the three or four examinations made during the year previous to the beginning of the treatment.[1]

I have also notes of three other patients who are taking the thyroids with benefit. One of them has acromegalia of rapid onset and typical form. No enlargement of the jaw is present, but the big hands and feet, rapid pulse, with tendency to palpitation and moderate muscular atrophy, place the diagnosis beyond question.

She came first to the out-patient department of the Massachusetts General Hospital, and was seen by Dr. G. M. Garland, who kindly gave me the opportunity of examining her. Later, she entered the

[1] The course of this patient since the original report was written presents some interesting features After she had been doing well for some months, the thyroids were omitted in order to test the result. For the first month after this there was little change in her condition; then the myxœdematous condition began to return, and by the end of a second month, when she presented herself for re-examination the first time, the change in the face was almost as great as ever. The œdema of the limbs, however, had not returned, and this is noteworthy, because an examination of the urine showed an entire absence of the albumin and casts that had been found previously at each analysis. Not only this, but the thyroid gland had enlarged very much in size, and the pulse had become quicker, suggesting the condition of partial Graves's disease, which was characteristic of the first period. The treatment was resumed, and in the month that has elapsed the patient has greatly improved. A sharp pain in the limbs came on, which was probably a symptom of the transition period, but this has now disappeared again under a continuance of the thyroid treatment.

wards, in the service of Dr. F. C. Shattuck, and there she improved somewhat under tonic treatment and sodium salicylate.

Some weeks after her discharge, however, I looked her up and found her still feeble and unable to work. Under fifteen grains of the thyroid powder every second day she has gained steadily, so that now, at the end of three weeks, she works with her hands for two hours daily.[1]

Of the other two cases, one stands nearer to acromegalia, the other to myxœdema, though in both the diagnosis is doubtful. The latter is of especial interest from presenting atrophy of the optic nerves, which is more common in acromegalia than in myxœdema, though seen in the latter disease (Hun and Prudden, Wadsworth, Jones). The former is under the care of Dr. G. C. Stearns, of Leicester, but is taking thyroids at my suggestion. A letter received yesterday reports that the improvement goes steadily forward, both as regards general strength and the appearance of the face and lips. There is a large swelling of the neck, probably a thyroid, which is diminishing in size under treatment; and, in fact, both patients consider themselves as decidedly better.

There are many questions of detail with regard to the new treatment by thyroid preparations which are of great practical importance. The following seem to me especially so:

Is the method by the stomach equally effective with that by injection, and is there anything to choose between the powder prepared by evaporation, the gland itself, and the extract precipitated with alcohol as recommended by Vermehren?

Must the dose by the stomach be larger than that by injection, and, if so, for what reasons?

[1] The recent history of this case has been very important. Some of the symptoms have continued to improve markedly, others not so much. The enlargement of the hands and feet has practically disappeared. They are, to be sure, very large, but the patient says they were always so, and I consider this point to be of decided interest in connection with the fact noted elsewhere in this paper, that patients subject to these trophic disorders sometimes show traces of the disease in their early years of life. Dr. C. L. Dana, of New York, in a paper read at the last meeting of the American Neurological Association, has pointed out that there is probably some relationship between giantism and acromegalia. Certainly my patient is an unusually large woman in all respects, and not only as regards her extremities, though these are particularly large. She can now wear boots that she could not get on at all when her symptoms were at their height. The other two patients seem to have distinctly improved in general health and slightly as regards their large features and extremities.

What is the cause and significance of the rapid loss of weight so often noted, and may it occur in ordinary obesity, or with healthy persons, under the use of thyroids?

What is the cause and significance of the other symptoms observed during the thyroid treatment, especially those of cardiac origin?

Are signs of renal irritation brought on or increased, and under what conditions?

Some of these questions can already be answered fairly well. The method by the stomach has not failed in any genuine case, and although one of the best of English observers at one time asserted that four or five times as large a quantity must be given to get the same effect as by subcutaneous injection, yet moderate quantities are sometimes so effective that we have no reason to conclude that any considerable part of the dose passes unabsorbed in most conditions of the stomach and intestine. Some good chemical or physiological test is, however, much needed to enable us to study these points and to compare the different preparations.

The loss of weight is an early sign of improvement, but it sometimes goes beyond the requirements of health; and this fact, coupled with the observations of Dr. A. Barron, of Liverpool, on the effects obtained in obesity,[1] suggests that the thyroid secretion may, under certain conditions, modify the tissue-changes even of healthy persons. A myxœdematous patient of Laache's lost more than nine kilogrammes, or about nineteen pounds, in three weeks, and my first patient must, at one time, have lost weight almost as rapidly.

Immediately after the injections, and even the stomach doses, of thyroid, there is sometimes a rise of temperature and pulse, increased secretion of urine, faintness or headache, and other symptoms; as the treatment goes on these symptoms may continue for a time, and may be associated with prostration, cardiac weakness, anginoid, neuralgic, or other pains (Laache), and even albuminuria (Laache).

[1] Dr. Barron has very kindly written to me that he has used the treatment in five cases of ordinary corpulence. One lost twenty-eight pounds in six weeks, three a moderate amount, and all lost more or less. I am trying it in two typical cases, but have no results to report as yet.

[Since this foot-note was written one of my obese patients has lost forty pounds in weight under the thyroid treatment. Another patient, who has been trying the same treatment under the care of my colleague, Dr. Coggeshall, has lost forty-seven pounds.]

(Note also the increase in signs of renal irritation in my second case.) It is striking and important that these unpleasant signs sometimes last for weeks after the suspension of the treatment.

Dr. F. C. Shattuck will no doubt call attention to an important case which he kindly asked me to see with him, where attacks of palpitation with anginoid pain continued for several weeks after the cessation of a rather active, though short, course of treatment which had in other respects been remarkably effective for good. The fact that these effects last so long after the treatment by thyroids has been stopped, and that, on the other hand, they have failed to appear in some cases where large doses have been given, or at any rate do not necessarily appear at once (Vermehren) (my first patient has taken repeatedly thirty grains of the powder without noticeable effect), render it unlikely that they are wholly due to a direct action of the thyroid extract regarded as a drug. At any rate, other explanations suggest themselves as more probable.

One is that through an increased excitability of the cardiac centres, or from some other cause, the heart is called upon for increased action at a time when its muscular walls are in an abnormal state, or when its coronary arteries, which are liable to be thickened, are not supplying it with sufficient blood; another, that the products which are absorbed so rapidly from the diseased tissues act as irritants. It will be remembered that two of Murray's cases died while their improvement was in full progress, from sudden heart failure brought on by trifling exertion. One of these patients was known to have had cardiac disease, the other was assumed to have had a fatty heart.

At any rate, the action of the thyroid extract is not in all respects the same in health as in cases of myxœdema. Fenwick finds that diuresis does not occur in health, nor usually with myxœdematous patients unless they are under some slight excitement.

As regards the question of renal irritation, I would call attention to my second case, where, in spite of rapid improvement in other respects, the number of casts in the urine increased, and to Laache's case in which temporary albuminuria came on.

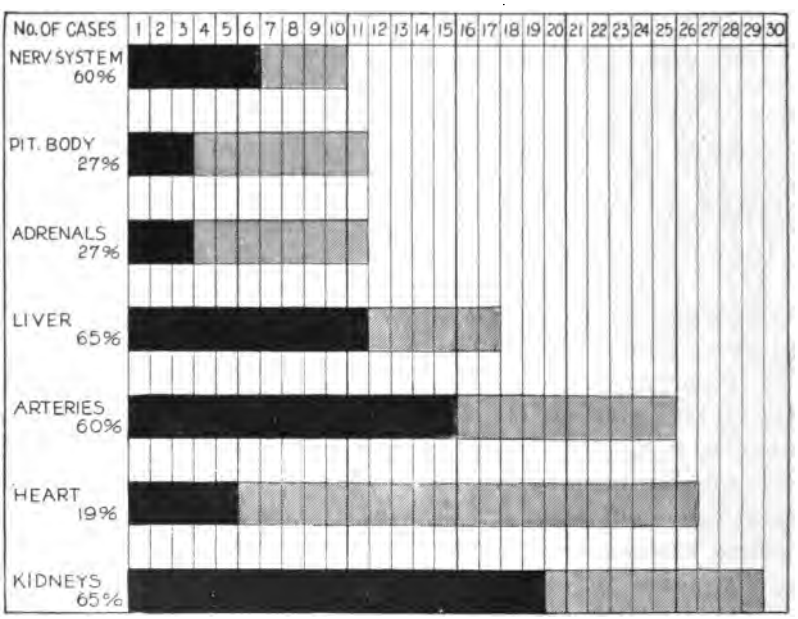
In another case, recently reported (Holman), the urine during treatment contained very large quantities of mucus.

Before leaving this part of the subject it must be noted that not only have the cases of myxœdema, successfully treated by animal

thyroids, been gathering like a rising tide, but that myxœdematous cretins have likewise been shown to be susceptible of a considerable degree of improvement (Bramwell, Affleck, Carmichael, Gibson, Vermehren, and others).

The point has not attracted as much attention as it deserves, that the "directly" hæmatopoietic functions of the thyroid, if they are

DIAGRAM 1.



The length of the columns indicates the number of cases in which the corresponding organs were stated to have been specially examined. The dark portion indicates the number of cases in which the organ was found diseased. The percentages are given in round numbers.

of real importance, ought not to be met by ingestion of the thyroid secretion. As a matter of fact, the anæmia of my first case does not seem inclined to pass away with the myxœdematous symptoms.

I shall confine myself, in what follows, to the pathological side of the subject.

To indicate, for reference sake, the percentage of frequency with which the different organs are diseased, I have arranged the results of the post-mortem examinations, including those published since

1888, in the form of a diagram, which, of course, must be taken as having only a relative and provisional value, since the autopsies are few, and the observations often incomplete and probably inaccurate.

I am not tempted to refer in detail to the varied anatomical changes to which the different organs are liable, because so little that is of fundamental importance has appeared since the able paper of Hun and Prudden, and the report of the Committee of the Clinical Society of London in 1888, and especially since the masterly review of the functions of the thyroid by Horsley in 1890. Two experimental researches are, however, worthy of special mention. One is that of Hofmeister, who removed in young rabbits the main part of the thyroid but not the glandules of Gley. This is supposed to leave the rabbits practically uninjured, and, indeed, their health does not apparently suffer, though the hair is apt to become a little coarse and the body relatively short and thick.

In fact, however, a series of other changes occur. The growth of the bones is checked; the epithelium of the convoluted tubules of the kidney is altered; the ovaries undergo a premature ripening, with an immense development of follicles. The hypophysis cerebri enlarges, but the spleen and thymus do not, and no histological changes were found in the central nervous system or in any of the abdominal organs.

The second research is by Capobianco, of the University of Naples, and has reference to the condition of the *nervous system* in the acute stage of the cachexia after thyroidectomy in dogs. They are fully confirmatory of the older observations of Rogowitsch, and show clearly how profoundly the circulation and nutrition of the brain, the medulla, the cord, and the nerve roots may be altered. The fact that other observers have found only circulatory changes, with œdema (see Horsley's paper) or swelling of axis cylinders (Kopp), shows that there are great differences in the degree to which these results are produced, but for this very reason we should scrutinize carefully before giving the verdict, "normal"; and the more so when we recall that changes in the electrical irritability of the cortex cerebri (Schiff, Horsley) and the peripheral nerves (Awtokratow, Schwartz) are found.

The discovery by Hodge, of Clarke University, that simple fatigue leaves its mark on healthy nerve-cells—even physiological fatigue, as

that of bees after their day's flight—should be borne in mind in this connection. Not only do these observations show the possibility of recognizing slight changes in nucleus and protoplasm, but they point out—what is too little regarded—that in estimating the effects of poisons or of other causes of impaired nutrition upon the central nervous system, we ought to know what conditions as regards exertion and fatigue had been present shortly before death. A man or animal who has taxed his poor or poisoned nervous centres will certainly have induced histological changes that otherwise might be wholly absent, and the exertion necessary for this result may be an amount which would ordinarily appear trifling.

It would be extremely interesting to see Hodge's experiments repeated on animals with the cachexia thyreopriva. The probability that positive evidences of an increased liability to fatigue would be found is foreshadowed by the experiments of Manfredi Albanese, which point to an increased susceptibility to fatigue on the part of the spinal cord in the serious condition which follows removal of the supra-renal capsules.

No doubt the case is different for the *chronic stages* of myxœdema and cretinism.

We do not know about liability to fatigue, but no histological changes were found, at any rate, by Hofmeister in his rabbits, or by such careful observers as Hun and Prudden in their cases of myxœdema. There are no histological changes, indeed, that are distinctly characteristic of the nervous centres of cretinism (Bourneville), though the arrangement of the convolutions is often peculiar.

Langhans and Kopp have made a careful study of the peripheral nerves after thyroidectomy and in cretinism, and have found a series of interesting and peculiar alterations in the endothelial cells of the perineurium and endoneurium, as well as in the lymph spaces and the bloodvessels, arranged in minute foci here and there, and especially common in the smaller nerves. The paper is one for histologists to discuss. Langhans at first thought these appearances to be peculiar to goitrous diseases, but this is very doubtful (Schultze, and Langhans himself).

The *blood* presents no constant changes except those of acute anæmia, and in the acute stages increased venosity (Horsley). The red cells have been found larger (Kraepelin), but also smaller than

normal; the proportion of whites increased and normal; eosinophiles increased in one case (Ehrlich); myelocytes present in one (Case I.).

As to the final cause and nature of the changes which constitute myxœdema and cretinism, that is a riddle the solution of which we can approach but cannot reach. That the blood becomes toxic is inherently probable, and is confirmed by the fact that although usually harmless[1] if transfused into healthy animals, it precipitates the cachexia in the case of animals deprived of their thyroids (Fano, Zander, Rogowitsch, Fuhr); while, on the other hand, the cachexia may be mitigated by the infusion of healthy blood. Gley asserts that the toxicity of the urine is also increased.

The skin, the kidneys, the ovaries (Hofmeister, Langhans), the liver, the heart and pericardium, and other organs and tissues, also show signs of irritation and sometimes of degeneration. This is doubtless sometimes mucinoid in character, but mucin has not always been found, even in the skin, and Jürgens shows how complex the change which we call mucinoid really is. We do not yet know whether mucin, when it does occur, is merely a sign of degeneration or whether it is itself a poison. That it is the chief or only poison in myxœdema is highly improbable.

There are, moreover, some phenomena which seem to be less easily explained as the result of irritation and degeneration than as evidences of a sort of variation in structure, analogous, perhaps, to that which follows castration.

The curious fatty tumors of the neck, so characteristic of myxœdema and myxœdematous cretinism, are not easily accounted for as results of irritation; the changes in the ovaries of Hofmeister's rabbits were interpreted by him as a sign of follicular hypertrophy or premature ripening; the myxœdematous cretin is not only a diseased and degenerate individual, but may be regarded as a different variety, and this appears even in his mental characteristics.

If one looks for other instances of alteration of structure with which to compare this, the most striking and, possibly, the nearest is that of eunuchism from castration, by which the bull is changed to the ox, and the cock to the capon. The analogy would be more significant if it could be shown by experiment that the effects of castra-

[1] Gley finds the blood of dogs after thyroidectomy to cause convulsions in rabbits.

tion could be prevented by frequent injections of testiculin; indeed, the analogy would not hold if the results of this experiment turned out negative. So far as I know, it has never been tried, but it seems to me a reasonable experiment, and a logical outcome of the suggestive observations of Brown-Séquard and D'Arsonval.

The next point to which I wish to call your attention is with regard to the incomplete or partial forms of the thyroid cachexias.

The attention of physiologists and pathologists has hitherto been mainly directed to the study of the diseases due to complete, or nearly complete, destruction of the thyroid; and the opinion is current that the functions of the gland may be as well performed by a part as by the whole, because it has been found that when a piece of any considerable size is left, the cachexia does not, as a rule, occur. Usually the remaining piece grows larger. Sometimes the accessory glandules, which are embryonic in character, also increase in size, and probably in efficiency, though they never grow to the size of the original gland. A compensatory enlargement of the hypophysis cerebri may also, it is thought, occur.

An additional argument for the view that a part of a thyroid will serve for the whole is apparently furnished by the recent experiments of Beresowski. He removed enough of the gland to cause cachexia, and found that in the course of a few days distinct processes of repair had set in, as indicated by karyokinetic division of the glandular epithelium. This hyperplasia ceased, however, long before the piece of the thyroid had reached the full size of the gland, and the reason for this was supposed to be that the vital needs of the gland had been met.

In spite of the large amount of truth in these generalizations, it is in order to inquire whether we really have sufficient grounds for believing that the thyroid is so unnecessarily large, and, if this is not the case, whether we may not learn to discover and relieve diseased conditions associated with a partial destruction of the gland.

It is important to note, as indicating the complex nature of the problem, that myxœdema may fail to occur even when the true glandular epithelium of the thyroid has been replaced by a cubical variety, apparently secreting no colloid; and, indeed, a small part of a gland so altered may suffice. This is illustrated by the history of a case of Graves's disease reported further on in this paper, and by

the experiments of Halstead and Welch upon dogs (see foot-note on page 350, and discussion).

As regards the argument drawn from the cessation of the compensatory hypertrophy at a certain point, it seems to me extremely improbable that the amount of regeneration is exactly proportional to functional requirements. The law of repair is more complicated than this, and that is indicated in the present case by the fact that Ribbert found a true regeneration to follow the removal of comparatively minute pieces of the thyroid (see also Neumeister).

It would be an interesting research to see how much, or rather how little, of the thyroid must be removed before changes in growth and nutrition can be detected, especially in the light of Hofmeister's experiments, which show that rabbits may present them in spite of retaining, by the aid of their carotid glandules, apparently good health.

The studies of dosage during the treatment of cretinic children by sheep's thyroids, will no doubt throw much light upon this matter of the amount of thyroid secretion needed for full compensation, and meantime some clinical evidence is already forthcoming to show that the amount of thyroid sufficient for life, and fair health, is not necessarily sufficient for all the functions of the gland.

Some of the most important forms of cachexia from thyroid disease, not severe enough to cause myxœdema, are the following:

1. The early history of myxœdematous patients sometimes gives evidence of the presence of analogous forms of degeneration.

Two cases have been reported within a few years (Loewy, Merklen), where myxœdema came on when the patients were between twenty and thirty years old; yet both were of dwarf-like stature, and presented certain slight mental peculiarities which, without stamping them as cretins, suggested a congenital deficiency of thyroid action.

Struck by these cases, I turned to the abstracts published by the Committee of the Clinical Society to look up the early history of the patients who became myxœdematous before their twentieth year; that is, cases of myxœdema belonging to the period antecedent to senile involution, and I found these histories, incomplete though they are, to be of much interest. Four such cases are recorded, and in at least three of them, in spite of the scanty record of antecedents, there had been

signs of degeneration, such as very low bodily weight; slight mental weakness; small, broad, and depressed nose; and extremely large tongue, indicating, perhaps, as in the cases first cited, a partial and unrecognized cretinoid state existing since childhood.

It is noteworthy that my first patient was not only anæmic and lacking in robustness, during her early life, but also showed some degree of the lethargic temperament which afterward became so very marked. The second patient was anæmic, and suffered from palpitation of the heart, even in girlhood.

2. Cretinism is a disease of many degrees, and some of the cretins show a fair intelligence, a few a first-rate degree (comp. Bircher, and a celebrated case cited by Langhans). Yet their skulls are of the type now considered as probably, or possibly, characteristic of thyroid disease. In myxœdematous cretinism, which is the lowest type, characterized by unossified fontanelles and synchondroses (occasionally premature ossification), dwarf-like stature, tendency to umbilical hernia, etc., the thyroid is greatly atrophied, sometimes absent. In other forms the atrophy is only partial (Hanau), and portions of the gland may look healthy. Furthermore, the removal of a cretinic thyroid may cause myxœdema (Bircher).

3. Goitrous persons, in districts where the disease is endemic, are generally of inferior type, though, of course, it is not certain that the thyroid disease is the cause of this.

In my second case, which is probably typical of others, it is worth considering whether the anæmia and debility of the pre-myxœdematous, but goitrous, period may not have been an early stage of thyroid cachexia. At any rate, myxœdema sometimes comes on quickly, but oftener slowly, and in the future it will be of great importance to learn to recognize the preliminary symptoms.

Another fact, of which we should never lose sight, is that myxœdema, or tetany, and perhaps other signs of the thyroid cachexia, may follow temporary disease of the thyroid, from which the patient eventually recovers, and may then pass away. Not only does this happen after partial thyroidectomy, but in the course of syphilis (Kocher), and as a result of ordinary goitre (*v.* Horsley's paper, *Brit. Med. Journ.*, 1890.)

As regards the question of the *compensatory hypertrophy* of the *hypophysis*, it is certainly true (Rogowitsch, Stieda, Hofmeister)

that thyroidectomy done on dogs and rabbits is usually followed by enlargement of the hypophysis, which comes so near the thyroid in structure and origin, and it would seem also that the thyroid may enlarge after removal of the hypophysis (Vassale and Sacchi). On the other hand, it is not accepted as certain that this enlargement means increase of functional activity.

To express a complicated matter in a few words, it is generally conceded that the hypophysis contains two kinds of cellular bodies, the "chromophiles," and the Hauptzellen (Stieda and Rogowitsch) or "nucleated protoplasm" (Schönemann).

When the gland enlarges there may be found an increase in the number of chromophile cells, or an enlargement of the Hauptzellen; and there is almost always an increase in the colloid contents of the gland. The increase of the chromophile cells has been thought (Lothringer, *Arch. für mikroscop. Anat.;* cited by Vassale and Sacchi) to be of functional significance; but Schönemann, on the basis of a careful study of the hypophysis of a cretin, came to the opposite conclusion, namely, that the chromophile cells are degenerated forms, and are finally to be converted into colloid.

Vassale and Sacchi have recently made an ingenious experiment which seems to favor the view of Schönemann. Removing the hypophysis from an ox, they divided it into two parts; and while one of these was preserved in alcohol for comparison, to indicate the normal histology, the other was introduced into the abdomen of a rabbit and left for three days, presumably to undergo slow degeneration. The chromophile cells in the latter half were found to have increased greatly in number.

The same observers deny that the mere increase in colloid matter ought to be taken as a sign of increased functional efficiency, either in the case of the hypophysis or the thyroid, unless it is accompanied with indications of active cell-growth of the glandular epithelium, with karyokinetic appearances, and this, they declare, does not occur in either organ simply from extirpation of the other. They do, however, regard the two organs as physiologically similar, and this is important for the pathology of acromegalia, which seems to me a disease kindred to myxœdema, though the bond may be but that of a Scottish cousinship.

Hofmeister's experiments, which are especially valuable because his

rabbits remained alive and well, and the hypophysis was given from three to six months in which to show its supposed compensatory growth, are confirmatory, as he thinks, of the observations of Rogowitsch and Stieda. He finds, as they did, not only an enlargement of the whole organ, but an increase in the size of the hauptzellen.[1]

The question is therefore still open for further research, but hereafter increased size cannot be taken as a sure sign of increased efficiency.

One suggestion thrown out by Hofmeister is worthy of comment, namely, that the large size of the sella Turcica, several times noted in cases of cretinism, indicates that the hypophysis had been hypertrophied. Klebs makes the same remark with reference to a case of acromegalia. As bony changes are, however, of regular occurrence in both of these diseases, the increased size of the sella Turcica admits of a different interpretation, and Schönemann distinctly notes that while the sella Turcica of his cretin was large, the hypophysis was rather small. Possibly it had been enlarged at an earlier period. Certainly the hypophysis is not always enlarged either in cretinism or myxœdema *at the period at which the post-mortems have been made.*

It is next in place to consider what other symptom-complexes, besides myxœdema, are associated with disease of the thyroid, and in what that association probably consists.

The diseases to be considered are exophthalmic goitre, acromegalia and certain forms of obesity.

1. The reasons for ranking Graves's disease among the thyroid cachexias were clearly set forth and ably championed by Moebius in 1891, and since then various writers have taken sides in the discussion (*v.* the abstracts by Moebius himself in Schmidt's *Jahrb.* for the past two years). Especially valuable are the monographs of

[1] There are several reasons for concluding that the colloid is not the important part of the thyroid secretion, but an envelope, or a by-product. Even its presence is not essential.

The valuable researches of Halstead and Welch, made some years ago, but not yet published, show that in the regeneration of the thyroid which follows mutilation, the histological character of the gland may undergo great change. The epithelium tends to become high and cubical, instead of flat, and the colloid to disappear. Canizzero (Deutsche med. Wochen., 1892, p, 184) has made similar observations. (See Discussion on Myxœdema, pp. 375-379 of this volume.)

A closely similar change has been noted by Councilman in a case of Graves's disease (referred to below).

Wölfler, of Graz, and the able paper of Wette, who has had a large experience with thyroid diseases in all their aspects, as assistant in the surgical clinic at Jena.

It must certainly strike anyone who studies the matter, that there is a certain likeness between the acute nervous symptoms of the first stage of the cachexia following either complete or partial thyroidectomy, and the nervous symptoms of Graves's disease; and, on the other hand, a certain contrast between the latter and some of the symptoms of chronic myxœdema. This argument from the comparison of symptoms does not, however, fully stand close criticism.

There is no real contrast, for example, between the sweating of Graves's disease and the dry skin of myxœdema, if the former is due, as is probable, to central excitation of the sweat nerves, and the latter to disease of the cutis.

It may be true that there is an analogy between the nervous erythism of the first stage of the cachexia thyreopriva and Graves's disease; but if this be so the cause is not evident. For in the one case we have to do with symptoms associated with absence of the thyroid, while in the other we have to do with symptoms associated with the presence of an enlarged thyroid, and actually curable, sometimes, by thyroidectomy. It is possible that irritation of the vagus and sympathetic is a factor common to both cases.

But there are other arguments of greater weight in support of the thyroidal theory of Graves's disease.

In the first place, myxœdema sometimes closely follows Graves's disease, or even, perhaps, accompanies it (Sollier; Von Jaksch, cited by Gauthier; *Clin. Soc. Reports;* my own second case), or the two diseases may occur in different members of the same family (Hadden, Virchow). Above all, thyroidectomy, or other operations on the thyroid, have proved of late years unexpectedly successful in the treatment of Graves's disease. About forty cases have been treated in this way, mainly by German surgeons, in all but three or four of which improvement or cure resulted. To this number I can add one case, which is, I think, the first to be reported in this country.

The operation was done in February, 1893, by Dr. J. C. Warren, at the Massachusetts General Hospital. The patient seems to be steadily, though slowly, improving. The whole gland seemed to

have been converted into a firm mass of adenomatous structure, with high cubical epithelium and without colloid, so far as examined. (Councilman.)[1]

The probability of a connection of some sort between Graves's disease and myxœdema is made stronger by including the case of acromegalia, which bears a certain likeness to both of the others, presenting the rapid pulse, the tremor, and the sweating of the skin characteristic of Graves's disease; together with trophic changes in the bones and integuments of the head and limbs analogous, perhaps, to those of myxœdema.

On the other hand, the experimental evidence with regard to the cause of Graves's disease, unsatisfactory as it is, favors rather strongly the view that it is due to the injury of certain nervous arrangements; and no theory should pass muster that does not attempt to account for the extraordinary manner in which practically the whole Graves's disease complex springs almost instantaneously into existence in persons with healthy thyroids under the influence of intense emotion. Sometimes, if the emotion quickly subsides, the symptoms may soon pass away (Gowers). My colleague, Dr. F. Coggeshall, has seen an exactly parallel case. The patient was a young girl, and the symptoms followed immediately on great excitement attending a whipping, but subsided in the course of a few weeks.

My own opinion as regards this complicated matter is that some such statement and explanation as that given by Wette is correct, but may be extended and modified. He thinks that goitre is one of the most important causes of Graves's disease, but not by any means the only cause; that the goitre may excite the cardiac and ocular symptoms, either by direct irritation of fibres of the cervical sympathetic or by indirect irritation of the sympathetic centres; and that many of the general nervous symptoms are due to the action of toxic substances formed by disordered metabolism within the diseased gland.

The explanation which would be most satisfactory is one which would include this, and at the same time cover the cases where Graves's disease comes on without antecedent thyroid disease, and I think that such an explanation can be hinted at if we do not take our physiology too narrowly.

[1] v. Foot-note on page 350 respecting the researches of Halstead and Welch.

The most probable hypothesis, though it can only be stated with infinite crudeness, seems to me to be as follows:

The Graves's disease complex, in common, probably, with most other neuroses, is the distorted correlative, or caricature, of one or several *physiological arrangements*[1] in which the nervous system plays the central part. The thyroid has an abundant and mobile circulation, and is supplied with nerves from the vagus and sympathetic. It is thus in position to inhibit (as occasionally seems to occur; see Wette) or to accelerate the heart, and on the other hand it is liable to swell almost like an erectile organ when the heart is acting strongly and its own vasomotor apparatus is weakened. When enlarged, the thyroid is liable to irritate the sympathetic and the other nerves in its neighborhood, and thus, in its turn, act as a centre of disturbance. These results almost certainly occur in many cases of thyroid disease (comp. Wölfler, Wette, and an able paper by Schranz, which I regret my lack of space to cite at length). It is even conceivable that one of the functions of the thyroid in health is to act as a regulatory apparatus for the heart, and it is further conceivable that there is a quasi-physiological connection of the following sort between the tremor and exophthalmus of Graves's disease, the disordered action of the heart, and the disease of the thyroid:

When a person is suddenly called upon for close attention, he fixes his eyes and holds his breath, his muscles stiffen, and his heart beats faster. If the attention changes to rage or fear, the eyes open wider, the heart palpitates, the voice changes, the hand trembles, the face and neck may become turgid from vasomotor paralysis, and even the circulation and secretion of the bowels may become affected.

As calm is restored these symptoms may pass gradually away, but the heart is slow to recover its tone. Judging from the fact that Graves's disease may immediately supervene on such events as this, we may assume as possible that the heart sometimes never recovers its tone, and that the delicate vascular apparatus of the erectile thyroid (which Schranz makes largely responsible for the origin of goitre) is also liable to suffer permanently.

Eventually, nutritive changes may occur (deposition of fats in orbits, etc.); and a morbid complex of symptoms, interdependent

[1] Compare Porritt, London Lancet, 1888, i. 164.

and correlated with each other, is formed, and becomes crystallized into what we call a disease.

When any member of this complex is induced, the others are likely, by association, to follow, and a tendency to the complex as a whole may possibly be inherited like a tendency to any other disease, or to a monstrosity. The exciting cause may be any one of many.

Tachycardia without exophthalmus or tremor occurs so frequently with ordinary goitre that it hardly deserves to be called abortive Graves's disease, but it may at least be an analogous affection.

The operation of thyroidectomy in Graves's disease—which, by the way, may be successful when it consists only in the removal of a sarcoma (Tillaux) or a cyst (Tessier, cited by Gauthier,)—may be supposed to act by breaking in upon the vicious circle of influences through which the disease is maintained. The extirpation of a part of the growth usually causes the rest to shrink (Wolff), just as iodine or external cauterization or electrolysis or division of the isthmus of the thyroid may cause the same result, and it is probably this and not the reduction of the thryoid secretion by removal of part of its secreting tissue that makes the operation of value. Mechanical and perhaps chemical irritations of the thyroid nerves are removed; a new set, as it were, is given to the action of the nervous centres, such as more favorable mental surroundings may give, and in favorable cases the old equilibrium is restored. It must not be forgotten that it is just as possible to produce this result from one side as from the other. Absolute repose for the nervous system, if it can be secured, as it sometimes can, is occasionally as effectual in causing the disappearance of the goitre as the thyroidectomy is in quieting the nervous excitement and the heart.

It is not probable that Graves's disease is related to the functions of the thyroid as a trophic organ, or, at any rate, that it is due to either an increase or a diminution of the normal secretions of the gland. That it is not due to an increase of the normal secretion is demonstrated both by anatomical considerations (coexistence with a small or practically small gland) and by the fact that the myxœdema, which is not compatible with an increased secretion of the thyroid, sometimes follows closely on the heels of Graves's disease, or even accompanies it. Neither can we refer it to a diminution of normal secretion, or we should meet it more often in connection with the invo-

lution of the thyroid. Moreover, it has often happened that all the symptoms of Graves's disease have come on with extreme suddenness, in consequence of strong emotion, in persons with normal thyroids, and have again disappeared almost as quickly. Again, it apparently is not cured by preparations of thyroid extract.

It is possible that disordered metabolism, due to a vitiated thyroid secretion, helps to keep up the nervous symptoms of Graves's disease, but this theory is in need of more evidence than it has yet adduced.

2. Acromegalia probably stands as near to myxœdema and diseases of the thyroid or kindred organs as Graves's disease, if, indeed, the bond be not closer.

It is more distinctly a sort of dystrophy than Graves's disease is, and affects much the same parts that are involved in myxœdema, namely, the bones and integuments of the face and extremities, and eventually, perhaps, of the whole body; for, as Klebs points out, the reason that the ends of the long bones show the growth the most is that the resistance there is least. Occasionally both myxœdema and acromegalia have an exclusively or almost exclusively hemiplegic distribution.

The growth of the hair and nails is apt to be impaired in acromegalia, though not to the same extent as in myxœdema, but, on the other hand, the skin often perspires freely, as in Graves's disease. Tremor is also common, and attacks of well-marked palpitation are of frequent occurrence.

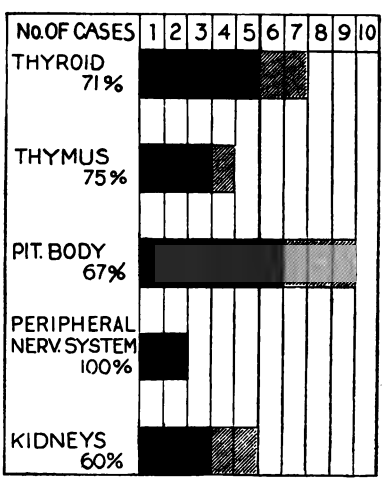
In the case of a middle-aged woman, recently under observation in the wards, and now in the out-patient department of the Massachusetts General Hospital, I found the pulse one morning 180, though from her phlegmatic appearance I should not for an instant have expected this. She had, to be sure, taken a dose of thyroid powder two hours previously, but on another occasion when she had not done this I found the pulse 120, and during her stay in the hospital, under the care of Dr. F. C. Shattuck, it ranged from 90 to 100, though she was kept perfectly still.

Klebs, who has studied the pathological anatomy of acromegalia quite extensively, explains the rapid pulse on mechanical grounds, believing that the disease originates in an affection of the thymus and that vascular changes occur by which the labor of the heart is

increased. It would not be fair for one who is no pathologist to offer a criticism of this theory in detail, but with the tachycardia of Graves's disease before our eyes it would seem more reasonable to seek a physiological than a mechanical explanation, as in the case of Graves's disease. I do not, however, mean to deny the importance of the thymus, or to maintain that acromegalia is distinctly of thyroid origin like myxœdema. I cannot dwell, for want of space, on the recent views of Marie and Marinesco, or on those presented in the monograph of Duchesneau, published in 1892.

Duchesneau calls attention especially to the occasional occurrence of muscular atrophy, but the theory by which he accounts for it, namely, pressure of hyperplastic connective tissue on the nerve roots, is not, I think, the true one. This atrophy is present in a typical form in the case recently at the Massachusetts General Hospital, though without other signs of nerve-root pressure, but so, also, is it

DIAGRAM 2.



Acromegalia—ten autopsies.

present in a case of Graves's disease which I have had the opportunity of studying closely for many years, and in several other reported cases of that kind. The explanation given by Duchesneau would certainly not apply here, and, on the other hand, the occurrence of

the atrophy in both these diseases forms another bond of union between them, though its nature is still so obscure.

I have said nothing as yet of disease of the hypophysis in acromegalia, and to save time I present the evidence on that point and others in the form of a table and diagram.

3. It is not certain that the dystrophic affections due to thyroid diseases are fully covered by myxœdema and the others that have been mentioned; and in this connection three communications, two by Dr. F. X. Dercum and one by Dr. F. P. Henry, in 1888, 1890, and 1892, are especially important. They describe three interesting cases, characterized by great and widespread hyperplasia of the subcutaneous fat, especially accentuated at certain parts of the body, and attended by pain and muscle-degeneration indicating the presence of neuritis. Perspiration was diminished or absent, and in this and other respects the cases suggested myxœdema. That which makes them especially interesting, however, is that the thyroids of two of the patients, who died while under observation, were indurated and infiltrated with calcareous deposit.

The name first suggested for this disease by Dr. Dercum was "A Subcutaneous Connective-tissue Dystrophy of the Arms and Back, Associated with Symptoms resembling Myxœdema." Dr. Henry first described the second of the three cases, and proposed the name "Myxœdematous Dystrophy." Dr. Dercum, in his final communication, says:

"All of these cases lack the peculiar physiognomy, the spade-like hands, the infiltrated skin, the peculiar slowing of speech, and the host of other symptoms found in true myxœdema.

"It would seem, then, that we have here to deal with a connective-tissue dystrophy, a fatty metamorphosis of various stages of completeness, occurring in separate regions, or, at best, unevenly distributed, and associated with symptoms suggestive of an irregular and fugitive irritation of nerve-trunks, possibly a neuritis. That this, however, does not embrace the whole truth is evidenced by such symptoms as the diminished sweating, the headache, and the contraction of the visual fields noted in Case I.

"Inasmuch as the swelling and the pain are the two most prominent features of the disease, I propose for it the name 'Adiposis Dolorosa.'"

Dr. Dercum further makes the good suggestion that the condition of the thyroid gland should be examined in all cases of obesity. The thyroid is rarely examined as a matter of routine, and least of

all microscopically, unless attention is especially called to it, so that our knowledge of the frequency with which this or that change is present, or as to the amount of variation in structure which is compatible with health, is still but slender.

A year ago Dr. F. C. Shattuck was good enough to ask me to see with him a very interesting case which deserves a place in some such category as this. Perhaps, indeed, it is a case of myxœdema, though, I believe, the improvement under thyroid treatment has not been very marked, except as regards the condition of the skin. The patient was a lady of about twenty, and the signs and symptoms consisted mainly in an increase in the subcutaneous fat, with changes in the skin not quite characteristic of ordinary obesity and somewhat suggestive of myxœdema, a change in the nutrition of the palms and soles, and a marked and peculiar discoloration and brittleness of the nails, associated with an irritability and excitability which finally developed into insanity. I trust that Dr. Shattuck will report the case at greater length.

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A CONTRIBUTION TO THE SUBJECT OF MYXŒDEMA, WITH THE REPORT OF THREE CASES TREATED SUCCESSFULLY BY THYROID EXTRACT.

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THE condition known as myxœdema has been so completely described in the report of the Committee on Myxœdema of the Clinical Society of London, and in the paper of Dr. Kinnicutt before the Association of American Physicians, that no further discussion of the symptoms is necessary.

I desire, however, to present the following cases to the Society as a contribution to the symptomatology and therapeutics of this disease by the use of thyroid extract. And in connection with these cases I desire to discuss briefly the mental condition present in all of my patients.

CASE I.—Female, aged forty-six, from Newcastle on the Tyne, England; a teacher by occupation, married, of good family history, and always in fair health until the beginning of the present illness, developed myxœdema in April, 1882, soon after the birth of her fifth child.

The diagnosis was made by Dr. Drummond, of Newcastle, soon after the onset. Her condition has been a sad one ever since, and various forms of treatment had failed to give her any relief.

She says that her disease developed gradually. The swelling of the skin began on the abdomen, and gradually extended to the face and extremities. As the swelling increased her skin became dry, scaly, and hard, and she often had formication in it. The nails soon became thick, horny, and curved, both upon fingers and toes. Her hair fell out. Her temperature from the first was subnormal, she never felt warm, and was exceedingly sensitive to the cold. This sensitiveness to the cold has been greater upon the right side of the body, on which side for a time her sensation of touch was much impaired, especially in

the fingers. Subjective sensations of a prickly character have been felt all over the body. She has suffered much from occipital headaches. There has never been any paralysis, but she says that when at her worst she has staggered somewhat in walking, and has not been able to walk any distance without much exhaustion. She states that the knee-jerks were at first exaggerated: they are now normal. From the beginning she had menorrhagia, for the relief of which, all other means failing, she submitted to ovariotomy, without effect upon the course of her disease.

Her mental state has been affected from the outset. She is a very intelligent and observant woman, and estimates her mental condition with considerable accuracy. She notices a very marked slowness in all her mental processes, but denies any abnormal persistence in one train of thought. She feels that

FIG. 1.

March 12, 1893.

there is an uncertainty in her judgment, and that she cannot think as clearly as she formerly did. She admits that her temper has become very irritable, and that she gives way to this irritation more easily than she ought to do. She has slept badly during her entire illness, though occasionally there have been periods during which she was unduly somnolent, and would sleep in the daytime. She denies having any delusions, but has been subject to hallucinations at intervals during her illness, having seen animals and people about her which perplexed her very much. She does not think that she has ever been insane, but admits that she was nearly so, her mind being constantly occupied by the hallucinations, and being so confused that no mental process could be clearly performed. Throughout her illness her memory has been treacherous, and it is not very clear with regard to dates at present. She has been timid in coming out of the house, and has been unwilling to meet people.

The preceding history was obtained from this patient in February, 1892, when she was first seen at my clinic at the College of Physicians and Surgeons,

and shown to the class. At that time an examination showed the typical appearance of myxœdema; the face, supraclavicular regions, and the entire body, including the extremities, being swollen and œdematous, though not pitting upon pressure; the color of the skin being a yellowish-white, and reminding one of wax; the hands and feet being pigmented, so as to present a dirty appearance; the hair being very thin; the nails hard and curved; the skin being scaly, dry, and wholly lacking in perspiration, the surface feeling cold to the touch. Her speech was thick and characteristic, the lips and tongue being much swollen. Her vision was good, though she said that at one time it was defective. Her hearing was good, though she said that at times she had been quite deaf. Her smell was poor, but the taste was keen. Her heart-rate was

FIG. 2.

May 14, 1893.

a hundred, and there was no murmur. Her arteries were soft, her respiration was regular and normal, though she says she often has dyspnœa upon exertion. Her digestion was good, she has had no difficulty in swallowing, though her tongue and gums have been swollen at times. Her teeth were in good condition. She has not suffered from indigestion or from constipation.

When first seen, her mental state was decidedly abnormal, she was easily depressed, and not at all clear in her statements.

She returned to the clinic on March 10, 1893, having been informed by her physician in Newcastle of the new cure for myxœdema. Her condition at this time was practically the same as in 1892. She was immediately put upon the glycerin extract of thyroid gland prepared for me by Dr. George W. Crary. Her photograph was taken on March 17th, and is herewith exhibited. (Fig. 1.) Her temperature was found to be $97\frac{2}{5}$ in the mouth. She was given six drops of the extract three times a day, and instructed to increase the dose one drop

daily. She has been seen once or twice a week up to the present time. The improvement began within ten days of the beginning of treatment, and has been progresive and continuous. This improvement has affected both body and mind, and in every respect the change for the better has been marvellous. The œdema has practically vanished, as may be seen from the accompanying photograph, taken May 12. (Fig. 2.) Her mental condition has improved to even a greater extent than her bodily state. She is bright and cheerful, quick in her thought and in her replies to questions, accurate in her statements, so that it is now possible to review her history and to fill out many points that were previously uncertain. Her recollection of her past sickness is more vivid now than it was before the treatment was begun. She is able to walk several miles a day, when formerly it exhausted her to walk eight hundred feet. She is free from pain, and sleeps well. The temperature has steadily risen from 97° under the treatment, and is now constantly normal. She has lost the feeling of cold which formerly annoyed her. She says that she is passing more water. Quantitative estimates of the urea have not been possible in this case, but it has at no time contained albumin or casts.

The dose of extract was increased until she was taking ten drops three times a day, at which point it caused a feeling of exhaustion, the pulse was found to be over a hundred, and the temperature 99½°. The dose was, therefore, reduced to eight drops, and has been maintained between eight and nine drops three times a day for the past month. This is the equivalent of half a gland daily.

CASE II.—Female, aged twenty-two, single. Father exceedingly nervous, mother an invalid all her life, died in 1890, of phthisis. No one in the family was known to have any disease resembling myxœdema, but the entire family on both sides is exceedingly neurotic.

The patient was never very strong, having had glandular swelling, chronic otitis media, headaches, and attacks of anæmia, ever since she was a child. She had measles at the age of fifteen, and has never been well since. The onset of the disease has been so gradual that it is impossible to say when the present symptoms first developed, but it is certain that in 1889 her appearance was noticed to be peculiar, the face being swollen and waxy in its pallor.

From 1889 until August, 1891, she was under treatment by various physicians for anæmia and chlorosis. In August, 1891, she received a severe mental shock, being with a relative who developed acute mania, and immediately after this she began to show mental symptoms which had not been present before. These mental symptoms consisted of hallucinations of sight, vivid at night, and causing her much alarm; she saw visions of angels, devils, and animals about her, and these kept her awake and gave her distress. At the same time delusions developed that she was a great sinner, that she had committed crimes, that she should starve. These delusions, usually of a melancholy type, persisted with greater or less intensity until the treatment was begun. The melancholy was so intense as to prevent her from taking any interest in things about her, and she would spend hours crying. She could not be diverted even

when her mental distress was over. One of the ideas which distressed her chiefly she has never been willing to state to any one; it was probably of a religious type. She was at times so excited that violence and suicide were feared by her friends.

She was first seen by me on February 19, 1892. I found a rather large, well-formed girl with dull facial expression, waxy complexion, œdematous appearance of the face, including the eyes, cheeks, and lips, which were markedly swollen, the facial lines being effaced and the naso-labial fold being much elevated. The lips were everted, and the mucous membrane of the mouth and tongue was pale, swollen and œdematous. The teeth, both of the upper and lower jaws, were much deformed, presenting a typical Hutchinsonian appearance, and being irregularly set in the jaw. The summit of each tooth was not more than half the size of the remainder of the tooth. The hair upon the head was thin, and had frequently fallen out, it is dry and brittle. The eyebrows and lashes were normal; conjunctivæ red and swollen; the skin of the face and the body was rough, dry and scaly. The skin of the hands half-way up the arms was dry, scaly, dark-brown, cracked, much wrinkled, and rough. The skin of the feet presented the same appearance as that of the hands; but the legs were not pigmented; there was no perspiration; the nails are slightly ridged longitudinally, and thick, but are said to grow naturally. The surface of the body feels cool, and she has a sensation of cold most of the time; when coming in out of the cold she feels a burning and numbness all over the body, especially in the extremities. The swollen tissues of the face and abdomen do not pit on pressure. Pulse was small, soft, and weak, about 65; heart sounds normal; temperature, 98°. Digestion is poor, there being little appetite and considerable constipation. She denies headache, but complains of vertigo and insomnia. Her menses are profuse, lasting six days, and occur regularly.

Her mental condition was found to be abnormal. She talks slowly and monotonously, the speech being very thick. Her memory is weak, and her answers to questions are not reliable. She was very emotional, cried and laughed frequently, and had to leave the room in a paroxysm of crying several times during my first visit. Talking excites her, and she complains of feeling much confused on any mental exertion. It is impossible to keep her attention fixed upon music or sewing or reading for any length of time, and she sits listless and brooding most of the day. At night she has hallucinations of sight and hearing, believes that she has visions of angels, and that people are talking to her constantly. She has the delusion that people around her can influence her by their thoughts; that she can read the minds of others, and that they can read her mind, and that she has been hypnotized without her consent. These delusions cause her great distress and much excitement at night. Motion is slow, reflexes normal, pupils act normally, optic disks pale but clear. The anæmia is very intense, blood corpuscles 3,600,000 to the c.m.

From February, 1892, until January, 1893, this girl's condition was practically stationary, the symptoms varying slightly from time to time in the onset, and the œdema changing somewhat from week to week. Warm baths and mas-

sage with oil, nitroglycerin one-one-hundredth of a grain three times a day, and sulphonal at night, seemed to have a better effect than any other form of treatment; ergot being evidently deleterious, and iron and arsenic producing no effect. In view of the appearance of the teeth, a course of mercury and iodide of potassium was carried out for two months without apparent benefit, and the physiological effects of iodide appeared when the dose reached forty grains a day. Several attempts at such treatment have been made, but have had to be given up on account of her susceptibility to the iodide of potassium.

On January 6, 1893, this girl was put on thyroid extract, the dose being five drops three times a day, increased gradually up to twenty drops three times a day. The improvement began three weeks after the beginning of treatment. At present, May 1st, her condition is markedly changed; the œdema has disappeared from the face and body and extremities, the tongue and lips alone being now affected. The skin is soft and no longer scaly and dry, she has some color, is well nourished, digestion good. Mentally, she is apparently well; she has no hallucinations or delusions, and goes about in society and to church, is able to practise, to sew, and to read; she still has slight feelings of depression, and cries a little. She is not quite natural in her manner, and is disinclined to talk about her mental symptoms, but in contrast to her previous state she is very much improved, and is almost well. Her temperature, which had always been subnormal, is still about 98° in the morning, but is now 99° at night, the pulse is 72, quite full and strong. During the use of the extract the amount of urine passed daily has increased markedly, and is now about two quarts. She has been out of the city, and no exact examination of the urine has been possible. It contains no albumin. The insomnia is the only symptom which persists, but mild doses of sulphonal or chloral are sufficient to relieve this. She walks three miles a day, and may be said to be fairly well. She is still taking sixty drops daily, of the thyroid extract, which is equivalent to a gland.

CASE III.—Female, aged forty-six years, married, has been under my observation since April, 1887, suffering from a variety of nervous symptoms due to the condition of myxœdema, which has been present ever since I first saw her, and which has undoubtedly been present since 1880, as even at that time she was suffering from many symptoms indicative of the condition of myxœdema.

The onset of the disease in this lady was very slow, and the symptoms have been very numerous and variable, the only constant symptoms being the condition of general swelling of the entire body, face, and extremities, extreme pallor with anæmia, deafness, great nervous excitability with occasional periods of depression without apparent external cause, occipital pain, albuminuria, and the peculiar scaly, dry condition of the skin with falling of the hair.

When I saw her first it was on account of the sudden development of right-sided facial paralysis, which has remained in part up to the present time, in spite of the most careful electrical treatment begun immediately after its onset, and continued for several months. The paralyzed muscles of the face

have gradually contracted so that very little asymmetry is now visible, unless she smiles or attempts voluntary movement upon the right side of the face. The deafness has varied slightly from time to time, though it always has been so extreme as to require the use of an audiphone. Her menses ceased six years ago, but at the time when they should occur every month she is nervous, depressed, and appears to suffer from a variety of symptoms of an hysterical character.

The diagnosis of myxœdema in this case was not made by me until 1892, the patient having been treated at intervals during five years for chronic nephritis, for anæmia, and for periodical attacks of melancholia and general nervous symptoms, the basis of which was supposed to be the chronic nephritis. She was seen during this time by three eminent consultants in New York, who concurred in this diagnosis. Nitro-glycerin was the only remedy which ever appeared to give her relief when suffering greatly, though many other things were tried. At present, now that the condition has nearly subsided under the thyroid extract, it seems clear to me that the symptoms were those of myxœdema from the outset. Yet the mistake in this patient was not without excuse, for she is a very large and very fleshy woman, and, therefore, the œdema, which has never been in her case extreme, was thought to be merely a condition of obesity, and the waxy appearance was thought to be due to the nephritis.

Yet, as the case is now understood, both the physical and mental symptoms, and the appearance, manner, and especially the speech of the patient can now be referred to the condition of myxœdema, formerly overlooked. In November, 1892, she came under my observation, after an interval of over a year, for she was suffering from a condition of great physical exhaustion, severe headache, insomnia, attacks of dyspnœa, and mental depression. There was a diminution in the amount of urine passed, and the urine was loaded with albumin, contained very little urea, and many hyaline and granular casts. The same condition of the urine had been noted in my history as having been present in June, 1887, for a short time. On examination of the patient in November, 1892, I recognized the appearance and speech of myxœdema, and it seemed to me quite clear that the kidney condition was merely one manifestation of the disease which I had formerly overlooked. With this conviction I began the treatment, by thyroid extract, as soon as my friend, Dr. George W. Crary, who had direct charge of the patient at the time, could prepare the extract; this was the first case in which I had used it.

The extract was prepared by Dr. Crary by obtaining the glands of the sheep at the slaughter-house, which he did with much difficulty, as it was found that the butchers, in killing the sheep, cut the throat of the animal at such a place as to divide these glands in half, and as in many sheep they are very small, weighing only ten grains, it was necessary to make a careful dissection of the two portions of the severed neck in order to find them. The butchers were unaware of their existence, and when requested to furnish the gland, uniformly produced the thymus gland, which they term the throat

sweet-bread. Dr. Crary succeeded in finding the real thyroid, however, and a microscopic examination was made by Dr. T. Mitchell Prudden of portions of the glands obtained, in order that we might be positive that we were dealing with the right gland. As Dr. Crary has supplied me with the extract in all the cases treated, I here produce his statement of the method by which it is prepared.

He dissects the glands, together with the fascia, from the trachea, and washes them thoroughly in a saturated solution of boric acid; he then dissects off the fat, obtaining the gland in its capsule with the vessels attached, and then washes this in a saturated solution of boric acid. From this solution the glands are taken, put into a sterilized towel, and with sterilized instruments the glandular tissue is carefully cut away from the fat, from the fascia, and from the vessels, so that only glandular tissue remains. This is then weighed. The glandular tissue from each sheep weighs from ten grains up to one-half ounce. Numerous glands of very large size which have been considered diseased have been found, but these are uniformly rejected. The glandular mass is then chopped very fine and mixed with glycerin, and allowed to stand four days. The glycerin is the German, doubly distilled glycerin, which is sterilized by heat for two days before being used. The extract thus obtained is very carefully filtered through sterilized cotton under pressure, and presents the appearance of a red syrup. It has been kept for a month without presenting any evidence of the development of micro-organisms.

The amount of thyroid gland in a drachm of this extract is twenty-four grains, which is equivalent to an ordinary sized gland. This extract has been given in drop doses to patients, the usual dose being thirty drops daily in divided doses, equal to half a gland.

The patient whose case we are now considering was given at the onset ten drops three times a day; within twenty-four hours the condition had changed, and the reaction was so intense as to give rise to much alarm; the temperature had risen to 103°, the pulse to 160; dyspnœa was extreme, and the mental distress very alarming. By the use of digitalis, atropia, whiskey, and strychnine these symptoms were combated, and at the end of twenty-four hours had subsided, not, however, without causing us great anxiety. It was evident that the patient had suffered from an acute poisoning, and that even thirty drops of the thyroid extract had produced very marked effects. When the thyroid extract was resumed, after an interval of a week, it was begun in five-drop doses twice a day, and this dose was gradually increased to ten drops three times a day, which is the largest dose she can take without manifest discomfort. From the time the dose reached eight drops three times a day the improvement began to be noticeable. At present, after four months' treatment, her appearance is wholly different from that to which I have been accustomed for the past six years. She no longer has the appearance of undue obesity, the natural lines of her face being now so perfect that we begin to realize how much her preceding appearance was unnatural, and the double chin, which was large, having disappeared. The skin, which formerly was dry,

rough, and scaly, is now soft and smooth, and she says that she is beginning to perspire naturally, a thing she has not done for ten years. There is a perceptible new growth of hair upon the head and in the arm-pits. The supra-clavicular swellings, which were very noticeable, have gone away entirely; her speech is very different in character, her facial expression has markedly changed for the better, her appetite and digestion are good; she is able to blow her nose. The urine has increased in amount; now contains much more urea and no albumin and no casts. The action of her heart is regular and moderate, and there are no longer attacks of faintness and dyspnœa.

Mentally, she is very much changed, the depression has entirely passed away, and she is in a state of comfort, interesting herself in her family, and acting in a perfectly normal manner.

REMARKS REGARDING THE MENTAL SYMPTOMS OF MYXŒDEMA.

One feature of these cases which has interested me greatly has been the type of mental disturbance which has been present and the great relief to the mental symptoms which has been afforded by treatment. Now that these patients have recovered they are able to discuss intelligently the phases of mental disturbance from which they have suffered. It is evident that the mental derangement has not been of the ordinary type seen in insanity. It cannot be classified under the head of melancholia, or mania, or confusional insanity, or hallucinatory insanity, or dementia, though it presents symptoms which might at different periods in the course of the disease remind one of any or all of these forms. All three patients had hallucinations of sight, occurring chiefly at night, of disagreeable figures and faces, sometimes animals, sometimes men, sometimes devils. One of them had hallucinations of hearing, and would listen for hours to what she considered were communications from the Deity. Two of them had delusions well systematized, but not constant, and all of them had suicidal impulses. The emotional state in all three was from time to time one of great depression and despair, yet in none was there any facial expression of settled melancholia, and in all it was possible to divert them for the time being and to produce interest and a smile, a condition very rare in true melancholia. In one of the cases occasional states of excitement almost maniacal in character were observed. In all the cases the general permanent mental state resembled mild dementia. There was a lack of interest in subjects, a tendency to sit listless and unoccupied, a feeling of effort on mental

exertion and actual inability to fix the attention or to conduct a train of thought; continuous conversation soon wearied them and the mental weakness was very noticeable in all. In all the cases the will power was deficient, there being a lack of energy, so that mental or motor effort was exceedingly disagreeable and all movements were very reluctantly performed. In all the cases there was defect of sensation, continuous use of the eyes producing great weariness; in two there was marked deafness, which varied from time to time in intensity; in all three taste and smell were slightly impaired, and in two the sensation of touch was impaired upon one side of the body.

It is thus evident that both the afferent channels of communication from the external world and the efferent paths of impulse to the muscles were in some way blocked by the disease, while the internal processes of mental association and activity were also hampered and deflected from their ordinary course.

We have to deal, then, with a group of mental symptoms in this disease similar in kind but quite different in their course from those characteristic of the ordinary psychoses, and quite as typical in their character of myxœdema as are the physical appearances so well known.

That these mental symptoms must be due to certain physical changes in the brain, probably similar in nature to those visible in the body, must be admitted especially in view of the relief of the mental symptoms by the treatment with thyroid extract.

The frequency of mental symptoms in this disease cannot be accurately stated, as in many cases recorded there is no reference to the mental condition. In the collection of 109 cases by the Clinical Society's Commission, the mental condition is described in only 46. In 18 of these there were delusions, in 16 hallucinations were present; 16 were said to have been at one time insane. In 56 out of 60 cases slowness of thought was noticed. I think it may be safely inferred that some mental symptoms are usually present in the disease.

In support of this statement I cite the following remarks made at a recent discussion upon myxœdema at Edinburgh, in February of this year, by Dr. Clouston:

"In eight cases of myxœdema it had been attended by mental symptoms of so severe a character that the patients had to be sent to his care in the asylum,

certified as insane. He had never seen any case of the disease where the mental power was not affected more or less. It was, of course, the exception for the mental symptoms to be so marked as to amount to technical insanity, but he thought that it might be assumed as one of the definite symptoms of the disease that all the functions of the whole brain cortex were altered in some degree. The slowness of voluntary movement, and the great delay in the mental reaction time, were the first mental symptoms. Then came a mental lethargy and hebetude. Along with this there was apt to be an irritability on slight causes, which meant that the mental inhibition was becoming impaired. All through the disease the diminution of control was a very marked symptom. This often led to acts of irrational violence. Then came a general enfeeblement of mental action—a mild dementia. Early in the disease a morbid suspiciousness, that often crystallized into delusions of suspicion, appeared. The intensity and the responsiveness of the affective faculty were found to be lessened. All the mental faculties become in time affected—volition, emotion, power of reasoning, and memory. Yet in no case had he seen complete dementia or acute delirious mania. He had seen suicidal melancholia with attempt of poisoning and refusal of food more than once. In one case the loss of control was shown by dipsomnia. The patients were easily affected by domestic annoyance or worry. Most of his asylum patients had sufficiently recovered in mind to leave the asylum and return home after a time, but none of them could be considered satisfactory mental recoveries. It would be one of the most interesting points connected with the thyroid-juice treatment, to see if that highest and most delicate of all organized structures in Nature, the brain cortex, could, after having been in a condition of disturbed nutrition for twenty years, completely recover its sound working. He had two cases now under treatment, one of them fifteen years' duration, where the mental symptoms were markedly abating. If such a complete cure resulted, it would be one of the most remarkable therapeutic results in the history of medicine. He had found a neurotic heredity to be common, but by no means universal, in the disease. There could be no doubt, however, that myxœdematous insanity—now, he hoped, to disappear forever, for all the cases would be treated and cured before they reached that stage—might arise without any neurotic heredity, simply from impaired myxœdematous nutrition of the brain cortex."—*Edinburgh Medical Journal*, May, 1892.

REPORT OF A CASE OF MYXŒDEMA.

By W. GILMAN THOMPSON, M.D.,
OF NEW YORK.

THE patient is L. S., female, aged forty-four years; single; born in the United States; by occupation a housekeeper. Her father died of apoplexy, her mother of heart disease, and a brother of phthisis. The patient's history is unimportant up to twelve years ago, when symptoms of the present disease

FIG. 1.

Before treatment.

first appeared. Menstruation has always been normal, and the menopause has not yet been reached. About twelve years ago, while living on Long Island, the patient suffered considerably from malarial fever, having repeated attacks during a period of two years. Shortly after the ague commenced she noticed that her face was becoming swollen, especially about the forehead and eyes. Soon she became weak, nervous, and very drowsy. The skin was dry and pale. Food distressed her, and she had unusual susceptibility to cold. Alopecia followed, and the patient observed some clumsiness in moving about, with great fatigue on physical exertion. These symptoms all developed within a period of three or four months, and have slowly increased in severity. Salivation has been occasionally present, and for a year or more

the patient has been unable to sew or read for any length of time on account of excessive lachrymation, although vision is normal. There has also been occasionally partial deafness and tinnitus aurium, attributed to taking cold. Recently palpitation has been a frequent and annoying symptom. Two years ago speech became somewhat slow and difficult, and the patient thinks that her memory has failed considerably. No depression of spirits. There has been recent slight swelling of the feet and legs, which have also often felt numb and cold. Slight dyspnœa, constipation, and anorexia have also been present.

Examination, on admission to the Presbyterian Hospital, April 5, 1893. Patient fairly nourished, anæmic skin, everywhere dry, loose, and inelastic; desquamation universal, but most marked on the legs and chest, where the skin is peeling off in large flakes resembling those of scarlatina. Hair absent in axillæ, very scanty on pubes, and very thin, dry, and brittle over most of the scalp, especially anteriorly and toward the vertex. Slight œdema of both legs. Face swollen, having peculiar waxy, doughy appearance.

FIG. 2.

Twenty-first day after beginning of treatment.

Lips thick, naso-labial fold obliterated, eyebrows arched, nose flattened, tongue greatly swollen—to the extent of half an inch at the tip. Speech thick and hesitating. Moderate salivation. Gums swollen and bleed readily. Hearing and vision normal. Mind apathetic. No visceral lesions apparent. Heart sounds distant, no valvular murmurs. Patellar reflexes diminished. Gait slow and labored. Pulse, 104. Respiration, 20. Temperature, 97.8° F. in mouth. Blood: hæmoglobin, 75 per cent.; red disks, 77 per cent. (on a basis of 5,000,000 per cubic millimetre).

Treatment. After keeping thepatient for four days under observation without treatment, she was given daily doses of five minims of a glycerin extract of the sheep's thyroid gland, prepared for me through the kindness of Dr.

George W. Crary. The temperature was then taken every two hours, and careful observations were made with reference to any reaction. As none followed, the quantity of extract given was increased by one minim with each dose, until a week ago the patient was taking twenty minims three times a day.

The patient has now been under treatment for fifty days. During this time the temperature has fluctuated three degrees, ranging between 97° and 100° F., most of the time being subnormal. At first the daily fluctuations amounted to 2½° or 3° F., but of late they have been only 1°. The hair has continued to fall out, but the extensive lamellar desquamation has ceased, and the skin in some situations, notably over the hands and arms, has become more elastic, softer, and much less dry. Ten days after the treatment was begun the swelling of the face, especially about the eyes, decidedly diminished, and the lips and tongue became slightly thinner. The patient's mental condition also improved considerably. The feeble circulation has not improved, but the patient sits up daily and moves about the ward. There has been a slight increase in the daily production of urea. Her family and several physicians who have seen her only at infrequent intervals unite in declaring that there is a positive improvement both in activity of mind and in facial expression. Seen from day to day the change is less noticeable, but the photographs which I herewith present offer favorable testimony. The first was taken before treatment, the second was taken on three weeks after treatment was begun. Several times the extract has been given hypodermatically in five-minim doses, but no reaction followed.

ANALYSIS OF THE BLOOD.

	Hæmoglobin.	Red disks.
April 12th	75 per cent.	77 per cent.
May 13th	72 "	62 "
" 24th	67 "	70.6 "

Dr. C. A. Herter has kindly furnished me with the following analyses of the urine and saliva.

URINE: SERIES OF EIGHT ANALYSES, EACH FROM A 24-HOURS' SPECIMEN.

Color normal and reaction acid in each.

	April 10.	Apr. 11.	Apr. 12.	Extract begun. Apr. 14.	Apr. 18.	Apr. 24.	May 19.	May 23
Volume in c.c. . .	300	290	430	420	590	560	1045	925
Specific gravity . .	1020½	1014	1016	1010	1012	1011	1011½	1013
Indican	Very strong	Strong	Neg.	.....	Strong	.....	Strong	Trace
Urea, grams . . .	7.775	5.014	8.267	5.409	9.005	6.448	11.152	10.562
" ratio . . .	35.2	34.8	38.6	42.4	40.2	40.8	43.2	
Uric acid, grams . .	0.221	0.144	0.214	0.127	0.224	0.158	0.258	
Preformed sulphate .	.....	0.369						
" " ratio	.....	4.6						
Combined sulphate .	.....	0.080						
Total phosphate . .	.....	.....	.....	.....	.....	0.632		
Chloride (sodium) . .	.....	.....	.....	.....	.....	2.062		
Kreatinin, grams . .	0.263							

ANALYSIS OF SALIVA.

Filtered to a clear solution, April 10, 1893.

	Parts per 1000.
Water	991.41
Solids	8.59
Soluble organic matter	5.16
" mucin	0.13
" inorganic salts	3.43

Dr. George W. Crary has kindly given me the following notes in regard to the preparation of thyroid extract which he made for me:

"The strength of the extract represents twenty-four grains of gland tissue to one drachm of glycerin. Strict surgical cleanliness is observed in all steps of the process, boric acid solution being, however, the only antiseptic used; heat sterilization being employed. The glycerin is Schering's, twice distilled and is sterilized before being used. The glands are cut up separately, and those diseased are, of course, thrown out. After standing four days, the extract is ready. After two months it seems to lose something essential, and I do not now use any older than that."

DISCUSSION.

DR. F. C. SHATTUCK: I wish to mention rather than report three cases of myxœdema, two in private, one in consulting, practice, during the past year. I shall report them fully at some future time.

Upward of a year ago a single lady, of twenty-nine years, was brought to me with symptoms dating back a number of years, but much aggravated within a few months. Her appearance had so changed that people did not recognize her. She had grown very stout, with supra-clavicular pads and peculiar trophic disturbances of the finger-tips, hands, and nails. Combined with this was a yellowish discoloration of the skin, most marked on the palmar and plantar surfaces, but also distinguishable on the trunk. Dr. Osler saw her with me on one occasion, and aptly compared the hands in color and surface to a goose's foot. Her mental condition was one of rather undue elation. Suspecting myxœdema, I sent her to Dr. J. J. Putnam, taking care that he should not know my suspicion. He was at first not disposed to agree with me, but has since that time, I believe, concurred. As soon as I could make arrangements to do so, early in May, 1892, I injected weekly a glycerin extract of a sheep's thyroid in three doses. The strictest precautions were observed, and no abscess formation resulted at any time. The injections were kept up for about three months. The skin improved very much, but from undue elation she passed into a condition of suicidal melancholia, which continued more or

less up to the present time. About two months ago she began to take Parke, Davis & Co.'s desiccated thyroid extract by the mouth, fifteen grains twice a day, and continued it for five weeks. It was then stopped on account of pains in the legs, and afterward resumed. She is essentially no better, though I feel that she has been fairly subjected to the treatment. In spite of this failure to gain, I believe the case to be one of myxœdema. Dr. C. F. Folsom had the care of her during my vacation last summer. Since then I have seen her only once or twice, as she lives out of town and is unable to be brought in. But I have been kept informed as to her condition.

The next case is that of a gentleman of sixty-nine years, whom I saw first two and a half months ago. His main symptoms were great sensitiveness to cold, constant watering of the eyes and running at the nose, weakness, and a tendency to diarrhœa. The skin of the hands in particular was very harsh; the lips were swollen, the lower pendulous. He said he was perfectly well until five months before. I thought I recognized an early case of myxœdema, and put him on the desiccated thyroid, 15 grains twice a day in capsules. Before many days he began to complain of pain in his legs and then in his chest near the cardiac region. The dose was diminished to 7½ grains twice daily. The myxœdematous symptoms rapidly abated, but I was soon compelled to stop the extract on account of very severe nocturnal paroxysms of pain like that of angina, demanding morphine hypodermatically, several nights, as much as two grains, in half-grain doses. This was accompanied by great tenderness just outside the left nipple, slight tenderness about this spot, and inability to lie on the left side. As the pain came on, the pulse would rise to 120, the normal rate being about 70. After three weeks' intermission I resumed the extract, at first 1 grain every second day, now 1 grain daily. His whole appearance has undergone a marked change, and he says he feels well—better than for two years. Both he and his wife now date his symptoms back further than they did at first.

The third case, that I saw in consultation, is of many years' standing, but was seen only very recently. Very marked improvement has already taken place, and her friends note the great change in her appearance, which was highly suggestive of Bright's disease. She has had much palpitation since she took the extract, 7 grains three times a week.

The special points to which I wish to call attention are the failure of the treatment thus far in a case which seems undoubtedly one of myxœdema, and the toxic symptoms noted more or less in all these—namely, pains in the legs, palpitation, and severe angina.

We are dealing with a very powerful agent, and should be very careful until we are more familiar with its dosage than we are at present. Among the many points upon which experience will enlighten us is the relation of the dosage to the duration or intensity of the disease. Finally, the descriptions as laid down in the books apply to old and very marked cases. As we learn to recognize the early stages of the affection we shall find that cases are pretty common.

DR. WELCH: I wish to say just a few words in regard to the subject of extirpation of the thyroid gland. I reported some years ago, at a meeting of this Association, some results that Dr. Halsted had obtained from extirpation of the thyroid gland in the dog. We found a singular alteration in the structure of the gland which has been referred to to-day as an hypertrophy of the gland. Perhaps no better name could be given to the changes, but the change is so complete an alteration of the structure of the gland that it is doubtful if anyone would, under the microscope, recognize in an advanced degree of the change sections of the organ as thyroid gland at all. So far as I know, no one except Dr. Halsted has accurately described these lesions in the gland. In these so-called hypertrophied glands the appearance of follicles has disappeared and the lumen of the follicle is filled up with papillary growths from the walls of the follicle. There is complete disappearance of the colloid substance from the lumen of the gland, and the low cubical epithelium has become high cylindrical epithelium and more granular than normal. This change, although called hypertrophy, is a very peculiar and remarkable alteration of the gland, which does not correspond to what one would understand by hypertrophy *a priori*. Another point is that this change, designated as hypertrophy, occurs as the result of interference of various kinds with the gland. Dr. Halsted has gone over the whole subject thoroughly, and has found that a very severe operative interference in the neighborhood of the gland, or a simple handling of the nerves or a ligating of the nerves in the neighborhood, or disturbing the tissues around the gland, frequently results in this same alteration in the gland. Then it occurred to us that this condition might be found normally in the dog's thyroid. We examined the glands of various dogs used for experiment in the laboratory, and found now and then, especially in cases which have been operated upon for intestinal suture and also for experimental peritonitis, that the glands presented this same change, although there was no operation done about the neck. Then we examined the thyroid gland in something over one hundred dogs taken in series at the pound of Baltimore, and found that a very small per cent. of the animals had this same enlargement and alteration in the structure of the gland. Of course, all of this means that the thyroid gland subserves some very important function, although it sheds no clear light on the nature of this function.

Another point which has been brought out since that report is the possibility of removing a great many times the weight of the normal thyroid gland by proceeding in this way: Dr. Halsted takes away one thyroid gland and a part of the other, but not enough to kill the animal. The part that remains behind hypertrophies. After waiting for a certain time, say six weeks or two months or longer, the remaining portion is bisected. This operation is repeated again and again, and a great many times the normal weight is taken away and absolutely no symptoms appear. During all this time the remaining portion of the thyroid is altered in the manner before described. I think that anything that bears upon these changes in the thyroid gland may prove hereafter of importance in the understanding of the function of the gland. Horsley

has gone over the whole subject very thoroughly, and it is quite clear from his review that it is not possible to draw any definite conclusion as to the functions of the gland.

DR. PUTNAM: With regard to the interesting remarks of Dr. Welch, we have recently had a patient with exophthalmic goitre on which Dr. Warren operated at my suggestion, removing about two-thirds of the gland. The part removed was afterward examined by Dr. Councilman, who found apparently the whole structure to be a dense homogeneous mass, and apparently the entire structure made up of what he called an adenomatous condition with high cubical epithelium, without any colloid anywhere. It is interesting to note that if only a very small portion of such a diseased gland is left, it seems to be sufficient, as Dr. Welch has said, to prevent the peculiar cachexia from coming on.

Dr. Starr referred to the fact that the sheep's thyroid was sometimes found diseased. Both Dr. Burr, of the Brighton abattoir, the inspector there, who was kind enough to secure the glands for us, and also Parke, Davis & Co., found that large numbers of them were diseased. Dr. Burr found about one-third of them diseased and these were rejected.

Dr. Starr also referred to the resemblance between some of these cases and cases of nephritis in their outward appearance, and that is very striking. In two cases, to my knowledge, the diagnosis of nephritis was made, and one of these I have already referred to. Then I know of two other cases where the changes were present in such form as to strongly suggest nephritis. They occurred in elderly people. It is a subject for investigation whether some of the obese elderly people whom we see with more or less of this œdematous condition are not really subjects of myxœdema, and capable of being improved by thyroid treatment. Dr. Shattuck's case, I think, was a man somewhat advanced in years.

In my first case which I reported the anæmia has been very constant. It has been very difficult to get her to have much of an appetite or to get rid of the very pale color which she presented. This is also a very interesting subject for investigation, whether the cause of the anæmia may not sometimes persist after the most striking myxœdematous conditions have passed away.

DR. STARR: The only word I have to say is in regard to the necessity of varying the doses of the drug somewhat in accordance with the reaction of the patient. That fact has been illustrated in the history of my cases. In one case under the care of a nurse the dose was run up to 22 drops of the glycerin extract three times a day, or 66 drops daily, which is equivalent to two and a quarter glands in a day. This was not followed by any apparent ill-effect. The patient improved constantly. The large dose was given owing to a misunderstanding between the nurse and myself, and I reduced it immediately, when I discovered it, to the original dose of 10 drops three times a day, and that dose has been continued. It seems to me that there may be a possible

idiosyncrasy in some of these patients. A fourth case, that I did not report, that is at present under treatment, began with 8 drops, and the patient is now taking 16 drops three times a day, without any decided change in her temperature. This seems to me to indicate that different individuals are differently susceptible to the thyroid extract, and in some cases, especially in Dr. Thompson's case, we did not begin to get any effect at all until the dose was run up to 18 drops of the extract three times a day. Referring to Dr. Shattuck's case, it would seem questionable whether it is proper to conclude that the thyroid extract would not do any good in such a case. It would be better to gradually increase the dose until you give pretty large doses—as large as you dare to give in connection with the case.

Recently in a discussion in Edinburgh on myxœdema, in the *Edinburgh Medical Journal* for May, 1893, out of a large number of cases reported in that journal—I think nearly seventy—there were but two cases of failure to relieve the patient by the use of this thyroid extract.

ON SPORADIC CRETINISM IN AMERICA.

By WILLIAM OSLER, M.D.,
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THE studies which have given to the thyroid gland the dignity of an organ with diseases of capital importance have come from practising physicians, experimental physiologists, and from surgeons—studies which "fitly joined together," have not only made clear dark problems in pathology, but have also raised a reasonable hope in the treatment of a group of hitherto hopeless disorders.

A relation between myxœdema proper and cretinism was hinted at by Gull in the title of his paper (1873) "On a Cretinoid State Supervening in Adult Life in Women," and clearly appreciated by Ord, in 1877, in a fuller description of the disease in which its connection with abnormal states of the thyroid gland was recognized. The remarkable cachexia found by the Swiss observers, Reverdin and Kocher, to follow certain cases of total extirpation of the thyroid, and the brilliant studies by which Horsley demonstrated the existence of an experimental myxœdema threw a flood of light on the whole subject, and enabled the Committee of the Clinical Society of London, in 1888, to reach the following conclusions: "That there is strong evidence that myxœdema, sporadic cretinism, endemic cretinism, cachexia strumipriva and the operative myxœdema of animals are severally species of one genus; that such clinical differences as exist between them are due to causes already sufficiently set forth; and that the one pathological fact common to all these conditions is the occurrence of morbid processes or of operations involving the annihilation of the function of the thyroid body."[1]

Having had at my clinic within a comparatively short space of time three cases of cretinism, and knowing that the subject of

[1] Report of a Committee of the Clinical Society of London, to investigate the subject of myxœdema. Clinical Society's Transactions, Supplement to vol. xxi., p. 199. London, 1888.

myxœdema was to be presented at this meeting, I thought the matter of sufficient interest to inquire as to the prevalence of the disease in this country. The report here made is based upon a careful search of the literature so far as it relates to the United States and Canada, and upon inquiries made of the superintendents of the Asylums for the Insane and of Institutions for Feeble-minded Children throughout the country, as well as of many friends.

As much misunderstanding exists as to the exact definition of a cretin, illustrated by the fact that at least one-half of the photographs sent me from different institutions did not belong to this type of idiocy, it may be well to define somewhat carefully the precise conditions to which this term should be applied. In the first place, there is no essential difference between the cases occurring in large numbers in goitrous districts and the sporadic cases. The term should be limited accurately to a form of idiocy associated with changes in or absence of the thyroid gland. The following statements are based upon the recent article of Horsley.[1] The important factor is the loss of the function of the thyroid gland, whether this results from congenital defect, progressive atrophy, or coarse changes which gradually annul its function.

1. Congenital cretinism is rare, and is usually associated with absence of the thyroid gland. The child rarely lives, but the changes presented are sufficiently distinctive for diagnosis. The supra-clavicular fatty tumors are well marked and the skin generally is thick and in folds. The limbs are short, the epiphyses swollen, while the shafts are much ossified. The skull is broad and short, the sutures open, and the basi-sphenoid junction is prematurely ossified, a point upon which Virchow laid great stress. This congenital variety may be difficult to distinguish from rickets. Degenerative changes, slow over-growth of the fibrous tissue, and a myxœdematous condition have also been met with.

2. Ante-natal and subsequent slow development of cretinism. Here the changes appear to have been initiated during fœtal life, but are slight and scarcely noticeable at birth.

"The infant shows no, or very slight, signs of intelligence, but the physical signs are less obvious. According to some, the majority at birth have a goitre,

[1] Tuke's Dictionary of Psychological Medicine. Art., "Cretinism."

usually of about an inch in diameter; the body is large, with disproportionate head and hands, and, what is more important still in connection with the similarity to myxœdema, in many cases the subcutaneous tissues appear œdematous; occasionally, according to the severity of the case, there is also non-development of the facial bones, a flattened nose, giving a stupid appearance, and a large thick tongue. The neck is short and thick. It is obvious that under these circumstances we have the same condition as that described above, only much less severe; the further history of these cases shows that the destruction of the thyroid gland continues, and the symptoms develop into the worst form of cretinism about to be described." (Horsley.)

3. Development of cretinism in early childhood. The infant may be perfectly normal at birth, develop naturally, and show no signs of disease until from the second to the fifth year. A majority of the instances of sporadic cretinism belong to this division.

"The child from being bright and normal becomes gradually less and less intelligent, and at the same time the physical appearances which have been summed up in the conditions before mentioned begin to assert themselves. The child does not increase in height, the limbs similarly do not lengthen, but remain short and thick. The trunk is broad and thick, there being also well-marked lordosis, so that the abdomen is prominent. In like manner the neck is shortened, the skull broad, the nose retroussé, the lips thick, and the teeth very imperfectly developed. The speech, from being clear becomes thick, the voice is rough and at times stridulous, the physiognomy is placid to stupidity, the skin is coarse, the hair becomes scanty and thin. There is well marked anæmia; the subcutaneous tissues have a peculiar kind of spongy or waxy feel, as if there were, so to speak, solid œdema occupying the connective fibres of the tissues.

"This condition thus produced reaches its height usually by the end of fourteen or fifteen years, so that by the twentieth or twenty-first year it has attained complete development, and thenceforward remains perfectly stationary until death. Hence, at the age of thirty the physical appearance presented is that of a young child, and the intellectual condition similarly does not advance beyond that of childhood." (Horsley.)

A majority of the cases of which I shall speak and which are illustrated in this paper belong in this division.

The adult condition of cretinism as seen in cases which have developed slowly, and have reached the age between twenty or thirty and over, is very characteristic. This "pariah of Nature," as it has been called, is a being degenerate both physically and intellectually; short in stature and childish in appearance. The height usually does not exceed that of a child from five to seven years old. The

skin is often rough, sometimes brown and stained, but in the sporadic cases more frequently of a chalky, earthy hue. In certain instances the subcutaneous tisssues are much infiltrated, so that the skin has a curiously waxy hue. Supra-clavicular folds of a fatty and myxœdematous character are common. The hair may be thick, and is usually confined to the head, even in adults; but in some instances there are traces in the axillæ and on the pubes. The face has an aspect of dulness and stupidity, though sometimes in the sporadic cases it is bright and smiling. The lips are broad and thick and prominent; the nose is broad at the base; the nostrils wide; the alæ very broad and pass without any special division into the naso-labial fold. The eyes are widely separated and sometimes present strabismus. The eyelids are often œdematous. In advanced cases, though they see things, yet they see without any intelligence, and the expression of the eyes adds very much to the impassive, immobile aspect. The tongue is often thick, large, and may constantly protrude from the mouth. The skull is large in proportion to the body and to the face. It is broad, brachycephalic, the transverse diameter approaching that of the antero-posterior. It is flattened in the forehead and frequently depressed and sloping backward. The two halves of the head are often asymmetrical. The sutures are often occupied by Wormian bones. The neck is large and short, and the thyroid gland may be enlarged or may be completely absent. The thorax is usually deformed in association with lateral or antero-posterior curvature of the spine. The abdomen is prominent and full. The limbs are extremely short, sometimes emaciated, occasionally deformed by rickets. The muscles are feeble, the hands and feet are large, the fingers thick and broad, and the nails often coarse and large, and may be rudimentary.

There are varying grades of cretinism, and just as we recognize complete idiocy, imbecility, and feeble-mindedness, so there have been described three degrees of this affection: cretins, which present in a most advanced degree the physical characteristics above mentioned, and are in addition deaf mutes with the vegetative functions alone active; semi-cretins with mental dulness, harsh guttural voice, expressionless countenance, and the physical condition similar to but less pronounced than that of the true cretin; and lastly the cretinoid condition, in which there is some degree of enfeebleness of the intelli-

gence, speech somewhat impaired, the physiognomy and the physical conformation that of the cretin.

The recognition of the condition of cretinism, though easy in advanced and typical cases, is often, I find, not clearly made. I judge this from the number of descriptive cases which have been sent to me as such, which in reality have been instances of various forms of idiocy. The important criteria are the physiognomy, the shape of the head, the stunted growth, and the condition of the connective tissues. The mental deficiency is less characteristic, presenting nothing not seen in instances of ordinary idiocy. The condition of the thyroid is uncertain. There are cretins with and cretins without goitre, while in others the gland seems entirely absent. The most satisfactory diagnostic feature is the condition of the skin and connective tissues, which, as Horsley suggests in the following words, should form really the basis of the classification:

"By excluding all cases in which the appearance of idiocy is not accompanied by any noteworthy changes in the skin or connective tissues we obtain a considerable delimitation of the condition which we ought to call cretinism, for by adopting such a plan of differentiation we necessarily leave out all cases due to direct injury or disease of the central nervous system, and which are included in the conditions classed by various writers under different headings, such as congenital idiocy, idiocy following encephalitis, idiocy coupled with porencephaly, etc., all being cases where we have destructive lesions or non-development of the central nervous system, especially of the cerebral hemispheres, and in which, therefore, we have a simple and direct destruction of the intellectual mechanism. Although such conditions may be naturally accompanied by want of development in the parts of the body which may happen to be paralyzed, etc., still there is no direct or certainly no general change in the connective tissues throughout the whole system, and secondarily in the nervous system, such as furnishes the basis of the present classification."

The pathology of the disease requires to be studied in the light of the more recent researches. In endemic cretinism the thyroid gland is very commonly enlarged, but in all probability functionless, and the intimate relation of the condition to goitre, particularly the marked influence of heredity as shown in the fact that goitrous parents are more likely to have cretinous children, shows the close interdependence of cretinism upon conditions of the thyroid. In the sporadic cases the thyroid is usually absent, and in all probability the progressive changes in the connective tissues, including the bones,

are associated in some way with the absence of the function of this gland.

HISTORICAL.

References to the existence of cretinism in America are found in Hirsch,[1] the *Dictionaire Encyclopédique des Sciences Médicales,*[2] the *Nouveau Dictionaire,* in the *Index Catalogue of the Surgeon General's Library,* and in the *Index Medicus.* Hirsch states that:

"Cretinism does not appear to be at all common except at a few points in all this region; at any rate it is stated by Barton that cases of it are rarely met with in the United States. Brown speaks of its occurrence in the valleys of Vermont; in Kneeland's account of the health of Massachusetts (for which State I have been able to learn nothing of the occurrence of goitre), it is stated that there are at least twelve hundred idiots and cretins in a population of about one million. Praslow also has observed somewhat frequent cases of cretinism among a tribe of Indians living near Cape Mendocino, in California, as well as among the Spaniards in the mountainous parts of Southern California."

These statements of Hirsch pass current in various works; thus Bury, one of the latest writers on the subject, in the *Cyclopœdia of the Diseases of Children,*[3] says: "In North America cretinism is not common except at a few points, namely, in the valleys of Vermont, Massachusetts, and in California." When we turn to the original sources for these statements, nearly all of which antedate 1850, we find, for example, the authority for the occurrence of the affection in Massachusetts the general statement of Kneeland,[4] that there are twelve hundred idiots and cretins in a population of one million. I can find no detailed observation in this article, and the term "cretin" was probably used in a loose way to indicate some variety of imbecility. So far as I can ascertain, the statements as to the existence of the disease in Vermont and New Hampshire rest on a paragraph in Buckminster Brown's article on cretins in Switzerland,[5] "simpletons or idiots are to be met with in the valleys of Vermont, New Hampshire, or Scotland." There is no reference to cretinism in Dorr's[6] account of the prevalence of goitre in the valleys of the Green

[1] Handbook of Geographical and Histological Pathology, vol. ii. (New Sydenham Society's Translation).

[2] Art., "Cretinism," by Baillanger and Kneishaber.

[3] Vol. ii. Art., "Cretinism."

[4] American Journal of the Medical Sciences, April, 1851.

[5] Ibid., 1847, ix. p. 111.

[6] New York Medical Repository, x.

Mountains. Trask, of Windsor, Vermont, speaking of the prevalence of goitre among the early settlers in the valleys, says: "In most countries goitre is connected with a species of mental imbecility called cretinism; but in the United States, thanks to God, it is a mere corporeal affection."

Praslow's account of the occurrence of the cretins in California I have not seen, but I have letters from several correspondents in that State who know nothing of its existence at present, while in the State Insane Asylum, at Stockton, Dr. Hoisholt tells me there are only two cases.

Barton,[1] whose essay on goitre, published in the year 1800, is one of the few systematic attempts to study the distribution of this disease in America, states:

"I have heard of some cases of cretinism among the Indians inhabiting the neighborhood of Sandusky. But such cases are undoubtedly very rare in North America. This circumstance, as I have remarked, is well calculated to show that goitre and idiotism are not necessarily connected with each other."

Here and there one meets with the assertion that cretinism occurs in Lower Canada among the French, but I have not been able to trace the allusion to its source or to verify the fact of its existence. Some years ago I looked through two of the large institutions for children in Montreal, and the Longue Pointe Asylum, without finding any, and two cases, supposed to be cretins, at Cacouna, proved to be remarkable rhachitic dwarfs.

The more recent literature descriptive of cases is also very scanty. Jacobi, in the *Hospital Gazette*, N. Y., vol. v., 1879, described briefly a case, the first on record in this country—a child of eight years. Johnson's paper, in the *Detroit Review of Medicine*, January, 1873, contains no statements about cretinism in America. Last year two cases were reported; one by Lloyd,[2] from the Philadelphia Hospital; the other by C. W. Townsend,[3] of Boston. Huber, in the discussion on Townsend's case, stated that the disease was not very uncommon among the children "in the tenement districts of New York, owing to the influx of immigrants," but no definite data are available as to the facts of its prevalence.

[1] Barton, Benj. Smith, Professor of Materia Medica in the University of Pennsylvania. "A Memoir Concerning the Goitre as it Prevails in Different Parts of North America." Pp. 93, Philadelphia, 1800.

[2] International Clinics, vol. ii., series 2.

[3] Archives of Pædiatrics, Nov., 1892.

ENDEMIC GOITRE.

Endemic cretinism occurs only in localities in which goitre prevails extensively, and the above observations, which have led in Europe to statements as to the prevalence of it here in endemic form, have been based in reality upon incidental references to, and studies upon, goitre, made for the most part in the early part of the century. So far as I can learn, the disease has not and does not occur endemically in this country. It may be interesting to note certain facts about goitre which I have gleaned in my inquiries, but which, however, refer to this malady only so far as it might be related to the existence of cretinism in a locality. Hirsch[1] is again our chief authority as to its prevalence; and, as he remarks: "Our information on the endemic occurrence of goitre in North America belongs for the most part to the early years of this century and is very fragmentary." Barton's memoir already referred to, and the articles of W. Gibson[2] and of Mease[3] contain the most authentic information as to its prevalence, from which subsequent writers have drawn their information.

Without entering into details which are available in Hirsch's work, it may be stated that goitre has been described as prevailing among the French Canadians along the Detroit River, and along the Richelieu River between St. John and Montreal; in the valleys of Vermont and New Hampshire; in the central parts of New York about the smaller lakes; in central Pennsylvania; in the mountainous districts of Maryland, Virginia, and the Carolinas; and in Alabama. From a majority of these localities we have no recent observations. I have written to a number of physicians in the towns of New England mentioned by Dorr[4] as very much affected, and so far have had only negative answers. Thus Dr. R. Clark, writing from Windsor, Vermont, one of the towns mentioned by the early writers, says that in the past fifty years he has not heard of its being very prevalent; and Dr. Emerson, who formerly practised at Chester, Vermont (a town one-half of the inhabitants of which were stated by Dorr [1806] to be subjects of goitre), writes that

[1] Op. cit., p. 149.
[2] The Philadelphia Journal of the Medical and Physical Sciences, vol. i., 1820.
[3] American Medical Recorder, Philadelphia, 1818.
[4] New York Medical Repository, 1806.

"during seven years' residence in Vermont I do not recall seeing more than three or four cases of goitre, and I do not think that it prevails to any special extent." Dr. R. J. Preston, of the Southwestern Lunatic Asylum, Marion, Virginia, has very kindly made inquiries as to the existence of the disease in some of the southwestern counties of that State, in which, as stated in Gibson's *Surgery*, the disease formerly prevailed, and here, too, it seems to have almost disappeared. Dr. W. Taylor, of Talladega, Alabama, who is the authority quoted by Hirsch in support of the statement that there is a "good deal of it" in the northern counties of that State, writes (1893) "since that time (1854) my views on the subject have been greatly modified. With a much larger population there are now really fewer cases of goitre to be found in Talladega and adjacent counties than in the earlier period of their history . . . . the fact remains that there has been a great decrease in the prevalence of goitre during the past thirty years, and the percentage of cases will not surpass the average in other States and communities."

In the Province of Quebec cases of goitre are by no means rare, and in Montreal the disease is certainly more frequent in hospital practice than in Philadelphia or Baltimore. I have no information of any localities in which it could be said to be endemic, attacking a very large number of persons. In the neighboring Province of Ontario, in the limestone regions at the end of Lake Ontario, the disease is very prevalent. In response to my inquiry about cretins, Dr. C. K. Clark, of the Kingston Asylum, mentions the extraordinary prevalence of the disease. Thus in an asylum population of about 600 there are 288 cases of goitre. He writes:

"The goitres are generally developed when the patients are admitted to the asylum, and it is rarely, indeed, that we see recent cases unless among the employés. After studying the subject carefully I have come to the conclusion that Eastern Ontario is a distinctly goitrous district, and I do not believe that outside practitioners have given the matter any attention. It is difficult to get accurate statistics even from asylums, and for this reason I have never published the returns sent in from nearly every hospital for the insane in America. A superintendent would answer my circular and state that his institution was without goitrous patients. I would go to his institution myself and probably find twenty or thirty goitres. The inference was plain, and when institutions side by side gave returns showing marked differences the inference was plainer still.

"Outside practitioners about Kingston have written nothing of interest in connection with the subject, but I find goitre prevalent even among the lower animals; most of the curs about the asylum have goitres, some of them so large that anyone can notice them. The tendency to this disease seems to run in certain strains, and the young of some families of dogs and horses are invariably goitrous. In two cases of human beings goitres have proved fatal through pressure. At one time I was inclined to believe that mental disease might be the factor determining the presence of goitre in so many of our people, but am now convinced that this alone will not account for the condition of affairs at the Kingston Asylum. The goitres met with in the insane are almost invariably incurable, probably because of long standing. Those occurring in employés are easily cured by ordinary methods of treatment. With some there seems to be a hazy idea that people coming from about Loughboro Lake have goitre more frequently than others in this district. There is nothing to show that such is the case, and the disease seems to be common and widespread throughout Eastern Ontario."

There are no cases of cretinism in the Kingston Asylum. Altogether, the evidence at command favors the view that in the regions of Virginia, Alabama, and Vermont in which goitre was formerly endemic, it is now very rare.

Endemic cretinism does not exist, we may say, in the United States or Canada, nor is it at all probable from what we can learn, that it has ever existed. My inquiries have not extended into Mexico, nor, indeed, into New Mexico, in which it is stated that both goitre and cretinism occur.

SPORADIC CRETINISM.

Independently altogether of the occurrence of endemic goitre, cases of cretinism are known to occur here and there in all civilized countries, and the inquiries which I have made in this country relate particularly to the existence of this form of the malady. Its rarity may be gathered from the fact that up to date, so far as I can ascertain, there have been but three cases put on record.

My attention having been called to the subject by the appearance in rapid succession of three cases at the Johns Hopkins Hospital, I thought it would be of interest to the members of the Association, particularly in connection with the discussion upon myxœdema, to ascertain somewhat more accurately the prevalence of the disorder. Accordingly I sent out letters to all of the asylum superintendents

in the United States and Canada, and to the various institutions for feeble-minded and idiotic children, asking information as to the existence of the disease. I wrote also to physicians practising in various localities in which it had been stated that goitre prevailed endèmically. Among the replies which I received were descriptions of many cases of idiotic children which were evidently not cretins; but, in addition to the hospital cases I have referred to, there were eight well characterized examples, the description of which will be given. In addition, from various superintendents there were statements as to the existence or occurrence of five or six other cases.

The interest in the subject is at present a very practical one, inasmuch as the observations on the beneficial effects of thyroid feeding have been shown in several cases, particularly in those seen within the first three or four years in life. I have at present two cases under treatment, but both for such a short time that it is impossible to say as to the changes in the condition.

CASE I.—M., aged (now) two years and three months, was brought to me first from the Eastern Shore of Maryland, January 10, 1892. The parents (first cousins) are healthy and strong. No hereditary ailments on either side; no members of the family have had goitre. The patient was the second child; the labor was easy, and she throve well. Nothing special was noticed about the child until the end of the first year, when it was suspected something might be wrong, as she had not cut her teeth, and did not attempt to walk or to talk. Throughout her second year she grew fairly well, but had several attacks of slight fever, and did not develop as other children, making no attempts to crawl or to walk, and seemed unnaturally quiet and dull. She did not cut the incisor teeth until she was nearly two years old. Within the past six months she has changed remarkably in color, has become very pale and waxy, and the face and limbs seem puffy and swollen. She has taken milk well, and has developed a little mentally; smiles, and attempts to repeat her own name when it is said, and has learned to say "mamma" and "papa."

Present condition. Under-sized child for her age. Aspect is very striking; color, pale; face, very broad across; the mouth is open; tongue protrudes, and is evidently enlarged; the lips are full and heavy; the cheeks very large, almost pendulous; the hair is long and straight; the eyes are blue; the sclerotics very pale; the eyelids glossy and infiltrated. The forehead is large, not badly shaped; the head well formed, rather prominent behind; the anterior fontanelle is not quite closed. She looks good-tempered, but takes very little notice, and smiles in a feeble way. The facial aspect is that of a cretinoid idiot. The muscles of the arms are feebly developed; the subcutaneous tissues much infiltrated; the hands are swollen and glossy—not

tense, and look œdematous, but the infiltration is firm, and only yields on prolonged pressure. The legs look large; the thighs present several folds; the skin looks glossy, and the subcutaneous tissues are much infiltrated. The skin over the dorsal portion of the feet is very glossy and tense, and on firm pressure pits with distinctness. The abdomen is distended and the superficial veins prominent. Palpation is negative; the edge of the liver is palpable about six cm. below the costal margin. The edge of the spleen is not palpable, nor does the organ appear to be enlarged. The thorax is well formed; no trace of rickety enlargement of the ends of the ribs; no evidences of rickets in the long bones. The apex-beat of the heart is just within the nipple line. There is a systolic murmur with the first sound, which is loud and intense at the pulmonary cartilage; the breath sounds are clear. There is no enlargement of the superficial lymphatic glands; the thyroid gland is not enlarged; the cricoid cartilage can be well felt, as can also the entire trachea as low as the sternum, and it can be taken between the two fingers quite plainly. Dr. Halsted thought he could feel the thyroid beneath the sterno-mastoid muscle. The percussion note on the first bone of the sternum is clear. The examination of the blood showed a moderate increase of leucocytes and some irregularity in the size of the red blood-corpuscles.

The condition was diagnosed as sporadic cretinism. As it was evident that the blood condition of the child was very much below par, she was ordered the syrup of the iodine of iron.

March 1, 1893. Patient brought again to-day. In the year and two months which have elapsed since I saw the child she has improved remarkably. She is not three-and-a-half years old. Her height is 75 cm. She looks more intelligent, takes more notice, and the facial expression is decidedly brighter. She tries to say a few words, and has begun to walk with a little assistance. The most striking changes are the disappearance in great part of the anæmia and lessening of the firm subcutaneous œdema, which was so striking a feature. She still has a little infiltration about the eyelids and cheeks. The limbs also look full, and they are firm. The skin is a little glossy over the hands and feet. The tongue does not protrude so often from the mouth, though when the face is in repose it is frequently seen protruding slightly. The face looks broad and full, and the expression and aspect is still cretinoid; Head is 51.5 cm. in circumference, the abdomen 54.5 cm. The neck is thick and short, and presents a large transverse fold of fat. The thyroid gland is not palpable, and below the thyroid cartilage the trachea can be felt with the greatest distinctness and grasped between the fingers down to the sternum.

The favorable reports from cases of sporadic cretinism treated with the thyroid extract encouraged us to try it in this case, and the child has been taking the glycerin extract of the sheep's thyroid in an amount corresponding to about a quarter of a gland in the twenty-four hours. No special change is as yet noticed after nearly a month's treatment.

Case II.—Emma, aged nineteen years; brought to the Johns Hopkins

Hospital by her mother, March 3, 1893. The family history is good; parents are not blood relations; no thyroid enlargement; no history of mental troubles. Patient is the second child; delivery was not instrumental; she was healthy when born; fat and well; nursed for nearly a year, and it was not until the end of this time that it was noticed that she was backward in development. She did not seem to grow and thrive as other children, though she took her food well, and was in other respects quite healthy. For several years it was thought that she was completely idiotic, as, though she took notice and seemed to know what was said to her, she did not walk or talk, but had to be held in the lap, and the tongue was constantly protruded from the mouth. She did not begin to cut her teeth until the third or fourth year. They decayed early and rapidly, and her second dentition did not begin until she was past her twelfth year. The anterior fontanelle did not close until after her eighth year. She did not begin to walk until her twelfth year. She has never learned to read or to write.

Present condition. Her height is three feet nine inches. She walks readily; the feet are turned out a little, and there is a somewhat waddling, uncertain gait, with the hands spread. The face has the characteristics of a cretin. The expression is pleasant; she smiles brightly, and looks good-natured, but has a childish, somewhat silly expression. She sits quietly, as a rule, with her mouth shut, but sometimes the tongue protrudes between the lips. The face is broad, and all the features thick and coarse. The nose is retroussé, the nasal orifices very apparent, and the alæ thick, and measure across the margins fully 5 mm. in thickness. The lips are thick and full; the cheeks prominent, large, and broad. In the upper jaw the lateral incisors are absent; the central incisors are of fair size, the enamel much eroded; the canines are small, also with defective enamel. The premolars and molars are small and much decayed. In the lower jaw the teeth are all present, but they are irregular and show the same character of defect. The roof of the mouth is much vaulted, the palate is not defective. The forehead is full, a little prominent in front; the head is long; the occiput projects, and it is broad immediately behind the parietal eminences. The occipital arches are much developed, and there are thick ridge-like projections at the line of the squamo-parietal sutures. The circumference of the head is 54½ cm.; from the tip of one ear to the tip of the other, 27 cm.; from the occipital protuberance to the glabella, 38 cm. The ears are well formed.

The neck is 36 cm. in circumference. The thyroid gland is distinctly enlarged; the left lobe more than the right. The hands and arms are well formed; there is no enlargement of the epiphyses. She uses her fingers well, and can feed herself and pick up small objects, but the movements are somewhat clumsy, and she is unable to dress or undress herself. The legs are firm and strong; not bowed. The gait is as above mentioned; she falls easily, and, as her mother expressed it, has no elasticity. She is flat-footed. The knee-jerks seem slightly increased. The body looks squat and full; the thorax is capacious; the back shows a moderate antero-posterior curvature.

The abdomen is large. Examination of the thoracic and abdominal organs negative.

She is well nourished, and the subcutaneous tissues are firm; do not pit, and there is no appearance like that of myxœdema, and it is only in the thickness of the features that the condition is suggested.

She talks a great deal; the voice is high-pitched, very difficult to understand. Some words she speaks clearly, and she talks and behaves very much as a child of two or three years. She is easily amused; showed with great pleasure and childish joy a little new ring, and is very fond of pretty things. She has a very good, musical ear; can sing several little songs. She is very good-hearted and generous, and always very anxious, if she has anything nice, that the servants, who are devoted to her, should share it. She is, however, self-willed, and does not like to be thwarted. She began to menstruate eighteen months ago.

CASE III. (Dr. Booker).—Minnie R., white, aged three and one-half years, came to Johns Hopkins Hospital Dispensary November 25, 1892. She was born in Lebanon, Pa., and lived there until one year ago, when she was moved to Steelton, Md. Born in natural labor; mother had only three hard pains; was a fat, healthy child up to second summer, when it was one year old, when had summer diarrhœa, about sixteen stools daily for a month; after that the bowels became regular, and child improved for a short while; then began to waste again without anything to account for it. She had no cough, no fever. There appears to have been no growth and no improvement since the attack of diarrhœa at one year of age, excepting the slight improvement which came on soon after the diarrhœa had been relieved, and lasted a short time. Parents are healthy, and no hereditary tendency. Mother has a younger child living and healthy; she never had a miscarriage. The child was brought to the dispensary on account of an almost constant crying, which had existed for three months. Appetite good; bowels regular; no fever; sleeps well.

Present condition. Child is thin, but not emaciated; is pale, with yellow tinge. Skin is dry, scaly, inelastic, in great folds, and appears much too large for the body. Numerous small lumps can be felt under the skin over the abdomen. Face has an idiotic or stupid expression; lips thick and coarse; tongue broad and thick, and protrudes a little between the open lips: child has only the four central incisor teeth, which are already decaying and nearly black. (The two lower incisors were cut in August, when one year of age, and just before the diarrhœa commenced. The following October was the time of slight improvement in the general nutrition of the child, and at this time the two upper incisors were cut; since then she has had no other teeth.) The nose is flat and broad; forehead low, and the head covered by thick, coarse, chestnut-colored hair. Strabismus in both eyes; fissures of the eyes very small. There is some enlargement in the neck in the region of the thyroid gland, but it is not certain that it is the thyroid. Also a thickening behind the sterno-cleido-mastoid over the clavicle. The limbs appear rela-

tively short; they are thin, and the skin is very loose and in great folds over the limbs. Hands are large, spade-like, and the skin rough and in folds over the hands. Right wrist has been slightly œdematous for several days. Abdominal organs do not appear to be enlarged; spleen not felt. Lymphatic glands of body enlarged. Weight, twenty-seven pounds; length, 69 cm. Temperature, 98.4° in rectum. Child cannot walk nor talk; mother said it could say "mamma" and "papa," but the child does not look intelligent enough for that. Blood examination: normal amount of white elements, some of which contain pigment; crescents and cellular bodies found.

The child was under observation until February, 1892. It was treated with quinine and arsenic, and for a while appeared to improve. It was able to sit up, which was more than it could do when brought to the dispensary. When last seen at the dispensary, February 10, 1892, it had about lost what had been gained, and was pretty much where it was when we first saw it.

The mother said the child had got all of its growth in the first year up, to the time it had the diarrhœa, that since then there appeared to have been absolutely no growth.

CASE IV. (Dr. Rotch and Dr. Bullard)—G. S., female; aged six years, American, parents not blood relations, not the subject of goitre. Does not speak; mental condition is much enfeebled. Circumference of the head is 46.5 cm.; measurement from occiput to roof of nose, 34.4 cm.; across the head from external meatus to external meatus, 29.3 cm. There is the general condition of infiltration like myxœdema of the skin. The thyroid gland is not to be felt. Circumference of thorax is 40 cm. The bones are somewhat enlarged about the epiphyses. The front teeth are good. (This case will be published in full by Dr. Rotch.)

CASE V. (New York Custodial Asylum for Feeble-minded Women, Dr. Brownell).—Sarah McG., aged nineteen years, American, parents temperate. She is 86.5 cm. in height; weight, 41 pounds. The complexion is sallow; voice discordant, harsh. She sleeps well; is good natured, and is seldom ailing; is a great favorite in the household. Largest girth of head, 52 cm.; from nose to occiput, 35.5 cm.; from ear to ear over vertex, 26.7 cm.; girth of neck, 29.3 cm.; girth of chest, 54.5 cm.; girth of abdomen at umbilicus, 62.5 cm. The abomen is protuberant and the chest is narrow; the legs are perfect, but the knees incline inward. The flesh of the hands and feet looks old and wrinkled; the teeth are a good deal decayed and notched. There seems to be complete atrophy of the thyroid gland; there is fulness in the supra-clavicular fossæ; there is marked curvature of the spine, both lateral and antero-posterior.

CASE VI. (Indiana School for Feeble-minded Children, Dr. Van Sweringen).—Louisa S., aged fourteen years, born in America, parents not related, no goitre in the family; nationality German. Height, 110.5 cm.; circumference of head, 56 cm.; from occiput to root of nose, 33 cm.; from external meatus to external meatus, 26.7 cm;; circumference of neck, 28 cm. The skin is loose and flabby, elastic and soft, very abundant. She is a deaf mute,

but appears quite intelligent. There is no curvature. The thorax is 57.3 cm.; abdomen, 68.6 cm. The limbs seem a little enlarged about the epiphyses. There is no goitre, and there is no trace to be felt of the thyroid gland.

CASE VII. (Syracuse State Institution for Feeble-minded Children, Dr. Carson.—Martha L. Y., aged sixteen years; parents Americans, not related.

FIG. 1. FIG 2.

Case V. Sarah McG., aged nineteen.

Height, 103 cm.; circumference of head, 54.7 cm.; measurement from occiput to root of nose, 32.5 cm.; across head from external meatus to external meatus, 34.4 cm.; circumference of neck, 34.4 cm. The subcutaneous tissues appear infiltrated and myxœdematous, and there are tumor masses behind the sterno-mastoid muscle. The thyroid gland is apparently absent. The circumference of the thorax is 67.5 cm.; of the abdomen, 71.2 cm. The bones of the limbs are a little enlarged at the epiphyses. The teeth are defective. She is feeble-minded, but appears to understand what is said; can only say a few words; answers yes and no. Is cleanly in habits; knows the names of objects, and can match colors.

Dr. Carson writes: "The child presents almost the characteristic features

described in cretins by Dr. Down, namely: absence of the thyroid gland, puffy swellings in the supra-clavicular space; skin of an earthy color, loose, and flabby, as if too large for its body; the nose flattened; the distance between the eyes exaggerated; tongue large; lips thick; cranium brachycephalic. She speaks only a few words in monosyllables, and, though occasionally stubborn, is usually of a placid disposition, laughs easily and heartily; is orderly and cleanly in her habits.

CASE VIII. (State Insane Asylum, Stockton, Cal., Dr. Hoisholt.)—Willie V., aged forty-two years; father was Irish, mother German; no note as to the presence of goitre. Height, 135 cm.; circumference of head, 55.3 cm.; from occiput to root of nose, 35 cm.; from external meatus to external meatus, 33 cm.; circumference of neck, 38.4 cm. The skin is very loose, and in places hangs in large folds. The head is brachycephalic. The skin in smiling is wrinkled. He is imbecile. The thyroid is not enlarged. There are no definite tumor masses above the clavicle; the spine is not curved. He is said to have been much brighter some years ago. The last three years he has had occasional epileptic fits.

CASE IX.—Johnny V., brother of the preceding case, aged forty years. Height, 127 cm.; circumference of head, 58.5 cm.; from occiput to roof of nose over the head, 29.5 cm.; from external meatus to external meatus, 38.3 cm. The skin is extremely loose; hangs in folds. On the scalp one may make a fold of four inches of superfluous skin; same on the neck, face, and back. The intelligence is very defective; speaks scarcely intelligible; he is not at all bright, except that he has, under the circumstances, a remarkable memory for names, remembering those of from thirty to forty patients in the ward. The thyroid gland is not enlarged.

The photographs of these two patients show marked brachycephalic heads, wide nostrils, the eyes wide apart, and the condition of the skin described by Dr. Hoisholt appears to be fairly characteristic.

CASE X. (Randall's Island Hospital, New York, Dr. Furness.)—Nellie R., aged fifteen years, born in New York State. Height, 76.3 cm.; circumference of head, 48.4 cm.; from occiput to root of nose, 30.5 cm.; from external meatus to external meatus, 31.2 cm. The skin is coarse and thick, and there are tumor masses above the clavicles. The thyroid is not enlarged. Circumference of the thorax, 54.7 cm.; of abdomen, 51 cm. It is distinctly pendulous. She can only stand with assistance. The epiphyses of the limbs seem somewhat enlarged. Intelligence is extremely slight, and she never talks, but can call the name of the nurse. She is affectionate in disposition, and recognizes the doctor by a peculiar shrill cry.

The doctor writes that the child looks about the age of three years; is unable to walk or to stand erect without support. The photograph sent illustrates a typical cretin.

CASE XI. (Inmate of the California Home for Feeble-minded Children; Dr. A. E. Osborne.)—I. N., female, aged probably thirty-five years; nationality unknown, supposed to have been Irish; no data about the parents.

Height, 108 cm.; circumference of the head, 56 cm.; measurement from occiput to root of nose, 35 cm.; circumference of neck, 38.3 cm.; circumference of thorax, 81.3 cm.; of abdomen, 84 cm. The face is broad and flattened; the skin rough, and hangs in folds over the body; the complexion is sallow; the hair very scanty and coarse; the teeth are defective, only half a dozen in the upper and lower jaws; no thyroid gland is palpable; the spine is slightly curved. The intelligence is of a low order, but her memory is good. The disposition is docile. She is tractable and affectionate, and forms strong attachments. She is quick to appreciate a favor, and has a fair sense of humor. The speech is slow and measured; the voice rather low and rasping. Respiration is slow, and the body temperature is below normal.

OPERATIVE MYXŒDEMA.

In connection with the subject of myxœdema, I am indebted to Dr. McGraw, of Detroit, for photographs, illustrating the following case, which, so far as I know, is as yet happily unique in American surgery, namely, one of operative myxœdema:

CASE XII.—The patient, George M., is now about thirty years old, and was operated on March 7, 1881. Complete extirpation of the thyroid. The photograph [exhibited] was taken March 30, 1893. A full description of the case will be published by Dr. McGraw. Suffice it to say here that there has been a gradual but progressive change in this young man since the date of the operation. The hair is scanty and coarse; the skin thick and rough; the subcutaneous tissues very thick; the integument and underlying tissues make great ridges on the back and on the hands and feet. The intelligence is good, but the action of the intellect is slow, and he is unable to do any continuous work or to study. He complains of fulness in the head and ringing in the ears when he stoops. Even in standing he is not steady on his feet, and has a tendency to fall. Temperature is normal; pulse, 70; respirations, 20. Heart's action is normal. Voice is harsh and squeaky.

DISCUSSION.

DR. WOOD: It seems to me possible that although cretinism is a rare disease in this country, it is more common than it would seem from the paper of Dr. Osler, simply because persons have not reported the cases which have occurred to them. At this moment I can recall two very positive cases which I have seen in my own experience entirely outside of any institution.

DR. GRIFFITH: What Dr. Wood has said is certainly true. For instance, I saw one case of cretinism during the past winter. The child was brought to

the children's clinic of the University of Pennsylvania and seen there by my clinical assistant, Dr. W. S. Carter, who sent it to my office knowing that I would be interested in the case. As it entered the room I asked how old the "baby" was, and was astonished to hear that it was already five years of age. It had the appearance of a child of eighteen months. Another glance showed at once what ailed it. It had all the appearance of typical cretinism. Dr. Carter will later publish details of the case. He has been recently making every effort to get hold of the child again, in order that he may give it some thyroid extract, but so far the efforts have been fruitless. The parents are healthy Germans living in one of the interior counties of Pennsylvania.

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